JOURNAL OF THE

NATIONAL CANCER INSTITUTE

TWENTIETH ANNIVERSARY
NATIONAL CANCER INSTITUTE

August 1957
Volume 19 • Number 2
A Publication of the
U. S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

JOURNAL OF THE NATIONAL CANCER INSTITUTE

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HEALTH, EDUCATION, AND WELFARE
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NATIONAL CANCER INSTITUTE
BETHESDA 14, MARYLAND
UNITED STATES OF AMERICA

DEPOSITED BY THE
UNITED STATES OF AMERICA

Commemorative Symposium XX

20th Anniversary of the National Cancer Institute

NATIONAL CANCER INSTITUTE ACT

Text of the Act of August 5, 1937, creating the National Cancer Institute and authorizing an appropriation therefor

[PUBLIC—NO. 244—75TH CONGRESS]

[CHAPTER 565—1ST SESSION]

[S. 2067]

AN ACT*

To provide for, foster, and aid in coordinating research relating to cancer; to establish the National Cancer Institute; and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That for the purposes of conducting researches, investigations, experiments, and studies relating to the cause, diagnosis, and treatment of cancer; assisting and fostering similar research activities by other agencies, public and private; and promoting the coordination of all such researches and activities and the useful application of their results, with a view to the development and prompt widespread use of the most effective methods of prevention, diagnosis, and treatment of cancer, there is hereby established in the Public Health Service a division which shall be known as the National Cancer Institute (hereinafter referred to as the "Institute").

SEC. 2. The Surgeon General of the Public Health Service (hereinafter referred to as the "Surgeon General") is authorized and directed for the purposes of this Act and subject to its provisions, through the Institute and in cooperation with the National Cancer Advisory Council hereinafter established—

(a) To conduct, assist, and foster researches, investigations, experiments, and studies relating to the cause, prevention, and methods of diagnosis and treatment of cancer;

(b) To promote the coordination of researches conducted by the Institute and similar researches conducted by other agencies, organizations, and individuals;

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*In 1944 all Public Health Service laws were consolidated, with needed revisions and additions, in a new law known as the Public Health Service Act (P.L. 410, 78th Congress, 2d Session). Most of the provisions of the original National Cancer Institute Act were incorporated in this new legislation.

(c) To procure, use, and lend radium as hereinafter provided;

(d) To provide training and instruction in technical matters relating to the diagnosis and treatment of cancer;

(e) To provide fellowships in the Institute from funds appropriated or donated for such purpose;

(f) To secure for the Institute consultation services and advice of cancer experts from the United States and abroad; and

(g) To cooperate with State health agencies in the prevention, control, and eradication of cancer.

SEC. 3. There is hereby created the National Advisory Cancer Council (herein referred to as the "Council"), to consist of six members to be appointed by the Surgeon General with the approval of the Secretary of the Treasury, and of the Surgeon General, ex officio, who shall be chairman of the Council. The six appointed members shall be selected from leading medical or scientific authorities who are outstanding in the study, diagnosis, or treatment of cancer in the United States. Each appointed member shall hold office for a term of three years, except that (1) any member appointed to fill a vacancy occurring prior to the expiration of the term for which his predecessor was appointed shall be appointed for the remainder of such term, and (2) the terms of office of the members first taking office shall expire, as designated by the Surgeon General at the time of appointment, two at the end of the first year, two at the end of the second year, and two at the end of the third year after the date of the first meeting of the Council. No appointed member shall be eligible to serve continuously for more than three years but shall be eligible for reappointment if he has not served as a member of the Council at any time within twelve months immediately preceding his reappointment. Each appointed member shall receive compensation at the rate of $25 per day during the time spent in attending meetings of the Council and for the time devoted to official business of the Council under this Act, and actual and necessary traveling and subsistence expenses while away from his place of residence upon official business under this Act.

SEC. 4. The Council is authorized—

(a) To review research projects or programs submitted to or initiated by it relating to the study of the cause, prevention, or methods of diagnosis and treatment of cancer, and certify approval to the Surgeon General for prosecution under section 2 (a) hereof any such projects which it believes show promise of making valuable contributions to human knowledge with respect to the cause, prevention, or methods of diagnosis and treatment of cancer;

(b) To collect information as to studies which are being carried on in the United States or any other country as to the cause, prevention, and methods of diagnosis and treatment of cancer, by correspondence or by personal investigation of such studies, and with the approval of the Surgeon General make available such information through the appropriate publications for the benefit of health agencies and organizations (public or private), physicians, or any other scientists, and for the information of the general public;

(c) To review applications from any university, hospital, laboratory, or other institution, whether public or private, or from individuals, for grants-in-aid for research projects relating to cancer, and certify to the Surgeon General its approval of grants-in-aid in the cases of such projects which show promise of making valuable contributions to human knowledge with respect to the cause, prevention, or methods of diagnosis or treatment of cancer;

(d) To recommend to the Secretary of the Treasury for acceptance conditional gifts pursuant to section 6; and

(e) To make recommendations to the Surgeon General with respect to carrying out the provisions of this Act.

SEC. 5. In carrying out the provisions of section 2 the Surgeon General is authorized—

(a) With the approval of the Secretary of the Treasury, to purchase radium, from time to time, without regard to section 3709 of the Revised Statutes; to make such radium available for use in carrying out the purposes of this Act; and, for such consideration and subject to such conditions as the Secretary of the Treasury shall prescribe, to lend such radium to institutions, now existing or hereafter established in the United States for the study of the cause, prevention, or methods of diagnosis or treatment of cancer, or for the treatment of cancer;

(b) To provide the necessary facilities where training and instruction may be given in all technical matters relating to diagnosis and treatment of cancer to such persons as in the opinion of the Surgeon General have proper technical training and shall be designated by him for such training or instruction; such persons while receiving training or instruction may, with the approval of the Surgeon General, receive a per-diem allowance to be fixed by the Surgeon General but not to exceed $10;

(c) To establish and maintain, with the approval of the Secretary of the Treasury, research fellowships in the Institute with such stipends or allowances (including traveling and subsistence expenses) as the Surgeon General may deem necessary to procure the assistance of the most brilliant and promising research fellows from the United States or abroad;

(d) To secure for the Institute, from time to time and for such periods as may be advisable, the assistance and advice of experts, scholars, and consultants from the United States or abroad who are learned and experienced in the problems involved in accomplishing the purposes of this Act;

(e) To make grants in aid for research projects certified by the Council pursuant to section 4 (c); and

(f) To adopt, upon recommendation of the Council and with the approval of the Secretary of the Treasury, such additional means as the Surgeon General may deem necessary or appropriate to carry out the provisions of sections 1 and 2 of this Act.

SEC. 6. The Secretary of the Treasury is authorized to accept on behalf of the United States gifts made unconditionally by will or otherwise for study, investigation, or research into the cause, prevention, and

methods of diagnosis and treatment of cancer, or for the acquisition of grounds or for the erection, equipment, and maintenance of premises, buildings, and equipment for the Institute. Conditional gifts may be accepted by the Secretary if recommended by the Surgeon General and the Council. Any such gifts, if in money, shall be held in trusts and shall be invested by the Secretary of the Treasury in securities of the United States, and the principal or income thereof shall be expended by the Surgeon General, with the approval of the Secretary of the Treasury, for the purposes prescribed by this Act, subject to the same examination and audit as provided for appropriations made for the Public Health Service by Congress. Donations of $500,000 or over in aid of research under this Act shall be acknowledged permanently by the establishment within the Institute of suitable memorials to the donors.

SEC. 7. (a) There is hereby authorized to be appropriated a sum not to exceed $750,000 for the erection and equipment of a suitable and adequate building and facilities for the use of the Institute in carrying out the provisions of this Act. The Secretary of the Treasury is authorized to acquire, by purchase, condemnation, donation, or otherwise, a suitable and adequate site or sites in or near the District of Columbia for such building and facilities, and to erect thereon, furnish, and equip such buildings and facilities when funds are made available.

(b) There is hereby authorized to be appropriated the sum of $700,000 for each fiscal year, beginning with the fiscal year ending June 30, 1938, for the purpose of carrying out the provisions of this Act (except subsection (a) hereof). Sums appropriated pursuant to this subsection may be expended in the District of Columbia for personal services, stenographic recording and translating services, by contract if deemed necessary, without regard to section 3709 of the Revised Statutes; traveling expenses (including the expenses of attendance at meetings when specifically authorized by the Surgeon General); rental, supplies and equipment, purchase and exchange of medical books, books of reference, directories, periodicals, newspapers, and press clippings; purchase, operation, and maintenance of motor-propelled passenger-carrying vehicles; printing and binding (in addition to that otherwise provided by law); and for all other necessary expenses in carrying out the provisions of this Act.

SEC. 8. (a) There is hereby authorized to be appointed in the Public Health Service, in accordance with applicable law, such commissioned officers as may be necessary to aid in carrying out the provisions of this Act.

(b) This Act shall not be construed as superseding or limiting (1) the functions, under any other Act, of the Public Health Service or any other agency of the United States relating to the study of the prevention, diagnosis, and treatment of cancer; or (2) the expenditure of money therefor.

(c) The Surgeon General with the approval of the Secretary of the Treasury is authorized to make such rules and regulations as may be necessary to carry out the provisions of this Act.

(d) The Surgeon General shall include in his annual report for transmission to Congress a full report of the administration of this Act, including a detailed statement of receipts and disbursements.

(e) This Act shall take effect thirty days after the date of its enactment.

(f) This Act may be cited as the "National Cancer Institute Act."

Approved, August 5, 1937.

DIRECTORS

NATIONAL CANCER INSTITUTE

CARL VOEGTLIN

Chief
National Cancer Institute
1938–1943

THE enactment of the National Cancer Institue law, followed by the formation of the National Cancer Institute, was the turning point from a pessimistic to a constructive, yet conservative, attitude toward the scientific solution of the cancer problem in the United States.

The relatively few scientists engaged in cancer research in a few laboratories, before 1937, received pitifully little financial and sympathetic support, as judged by present standards.

The one day meeting a year of the Cancer Research Society was attended by a very small but devoted group of members.

The American Society for the Control of Cancer spent practically all its efforts on educating the public in the early recognition and treatment of cancer.

All this changed radically in a few years after 1937. A rapidly increasing number of able scientists, representing many disciplines, became interested in the cancer problem and received liberal financial support. New Cancer Institues were founded in various parts of the country. Cancer research had finally come of age.

World War II temporarily slowed this progress, which was even more rapidly pursued after the end of the war.

May I close with my sincere congratulations to the National Cancer Institute for its many important contributions toward the solution of this complex and important public health problem.

CARL VOEGTLIN

ROSCOE R. SPENCER

Director
National Cancer Institute
1943–1947

TWENTY years is a short time in the life of any institution. I believe that the phenomenal growth of the National Cancer Institute, since its inception in 1937, is a significant and prophetic expression of the great organizing principle in living nature and, specifically, of man's will to live.

Congratulations from one who was privileged to assist at the birth of a great research institute.

ROSCOE R. SPENCER

LEONARD A. SCHEELE

Director
National Cancer Institute
1947–1948

THE twentieth anniversary of the National Cancer Institute is indeed a memorable occasion.

The directive by Congress to take steps to study the cause, prevention, and cure of cancer marked the beginning of a movement to relate a major part of Government research support to the major causes of crippling and death. At the same time, infectious diseases and other problems received increased attention.

The National Cancer Institute's program pioneered a method of support for Research Fellows and Trainees and by research grants, without undesirable Government control. The creation of a National Advisory Cancer Council of non-Government people, with veto power on the giving of grants, set a wise pattern of operation that has been followed in other Institutes of the U. S. Public Health Service and in the National Science Foundation program. A pattern was established in which the Public Health Service staff developed close, cooperative working relationships with the American Cancer Society and other voluntary agencies in the cancer field.

After twenty years of operation, the program continues to prove its success and is playing a major role in the ultimate solution of cancer problems.

LEONARD A. SCHEELE

JOHN R. HELLER

Director
National Cancer Institute
1948–

The National Cancer Institute: A Twenty-Year Retrospect[1]

J. R. HELLER, *M.D., Director, National Cancer Institute, Bethesda, Maryland*

THE National Cancer Institute was created by a bill drafted for this specific purpose, passed by the 75th Congress, and signed by President Franklin D. Roosevelt on August 5, 1937. By the terms of the Act it went into effect thirty days later.

From the beginning of the century to 1937, more and more people had become concerned with the cancer problem in the United States; and a few states had already passed legislation in an attempt to promote research or to provide more adequate care for cancer patients, particularly those in straitened circumstances. The American Society for the Control of Cancer was formed in 1913. A number of private donors had established trusts or endowments to finance cancer research either at a specific laboratory or to provide grants-in-aid to support projects at various institutions. The medical profession in general was taking a greater interest in the problem of cancer. In 1922 the Public Health Service, acting under its inherent powers, began research on cancer but the pace was slow and, although much new knowledge was accumulated, little of it was immediately applicable to the treatment of the cancer patient.

In Congress there was much interest in the subject, and, from time to time during the ten years immediately preceding the establishment of the National Cancer Institute, bills had been introduced in an attempt to have the Federal Government take a more aggressive lead in cancer work. This is not the place to review the legislative history of these bills, but it is of interest to know that Senator M. M. Neely, of West Virginia, has stated that the first such bill was the one he introduced in February, 1927. This bill would have established an award of five million dollars for the "discovery of a successful cure for cancer." The response to the publicity attendant upon the introduction of the bill soon convinced the Senator that this was not the proper approach to the problem, and he immediately began to seek advice from scientific sources to guide him in proposing other legislation. He, along with every other Senator, signed the cancer bill introduced in the Senate in 1937 by Senator Bone, which was one of the three bills that culminated in the passage of the National Cancer Institute Act.

[1] Grateful acknowledgment is made of the assistance of Miss Ora Marshino in preparing this article and in reviewing several other papers in this issue of the *Journal*.

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Outside Congress there also were many people who thought the Government should initiate a more extensive cancer program. Among these there was no one who backed his ideas with action as energetically and persistently as Dr. Dudley Jackson, of San Antonio, Texas. As a surgeon he had ample opportunity to witness the ravages of cancer. He had conducted some cancer studies of his own. Since 1928 Dr. Jackson had been trying to interest Government officials and others in certain types of cancer work that he thought could most appropriately be sponsored by a Government agency. It was due to his efforts that the Maverick bill, also one of those which resulted in the establishment of the National Cancer Institute, was introduced in the House in 1937. The National Cancer Institute Act was the final outcome of three bills and a House Joint Resolution introduced in the first session of the 75th Congress. The first two bills, which were identical, were introduced on April 2, 1937, by Senator Homer T. Bone and Congressman Warren G. Magnuson, of Washington. On April 29, 1937, Congressman Maury Maverick, of Texas, introduced his bill, and on June 24, Congressman John F. Hunter, of Ohio, introduced a House Joint Resolution containing exactly the same provisions as the Maverick bill, except that it would have made the proposed new cancer center a memorial to Thomas Jefferson.

Although the introduction of the Bone-Magnuson bill preceded Congressman Maverick's by some three weeks, the latter had been in the process of preparation for many weeks previously. At the suggestion of Dr. Dudley Jackson, Congressman Maverick had sought the assistance of the Public Health Service in drafting his bill and a number of circumstances had combined to delay this work. The Bone-Magnuson bill called for an annual appropriation of one million dollars to support a national cancer program. The Maverick bill called for an initial appropriation of 2.4 million and one million dollars annually thereafter. In 1937 those were large amounts indeed. Although both bills provided for a very extensive program to be carried on by the Public Health Service and conferred broad powers upon the Surgeon General, the terms of the Maverick bill were much more specific and provided, among other things, for the establishment of a national cancer center in the National Institute of Health.

There were many factors favoring the enactment of Federal cancer legislation at this time, and the fact that the Bone bill was sponsored by all ninety-six Senators assured its passage in the Senate if it received favorable action by the Committee on Commerce, to which it had been referred. Such consideration seemed likely, since the Committee chairman was Senator Royal S. Copeland, a physician, from New York. Although the Maverick bill carried no imposing list of sponsors, there was no real opposition in the House to its enactment. This bill, as well as the later House Joint Resolution introduced by Congressman Hunter, was referred to the Committee on Interstate and Foreign Commerce, headed by Congressman Clarence F. Lea, of California. The Committees expedited action on the bills by arranging for a joint committee hearing at which all

the bills would be considered. This was held on July 8, 1937, before a cancer subcommittee made up of five Senators and six Representatives from the respective Committees and chaired by Senator Copeland. The hearing lasted but one day. The several witnesses expressed various opinions as to the elements and administration of a Federal cancer program, but no opposition to the program itself. Following the hearing, a revised bill was drafted, and before the end of the month it had been passed both by the Senate and the House. It was signed by the President on August 5.

The law as passed represented no single individual's ideas for a Federal Government cancer program but was a composite of the best thinking of many people, in both the field of cancer work and in government administration. That their thinking was sound and forward-looking is attested by the fact that the legislation has stood the test of time. As yet, Congress has had little occasion to modify the basic provisions of the law, other than to lift the ceiling on appropriations and to change the size and composition of the National Advisory Cancer Council.

The law placed the new Institute in the Public Health Service, then a Bureau of the Treasury Department, where, understandably, it was received with somewhat mixed reactions. There were some who felt that the establishment of an entire Institute devoted to one disease gave it undue emphasis and might serve to lessen the interest in other diseases, which, in their opinions at least, were equally important. Also, some scientists found it hard to reconcile themselves to the advent into the laboratory of the strange new programs which the Institute was directed to initiate. Even the most public-health minded could hardly escape the occasional thought that public acclaim might turn to disappointment if the new Institute did not quickly make discoveries that could be applied in the treatment of cancer patients.

In 1937 there was little to encourage the most optimistic to think that the answer to the "riddle of cancer" was just around the corner. Rather, there were some who felt that the problem might be unsolvable; and most cancer researchers knew that, barring some fortuitous event, the chance for an early discovery of a specific "cancer cure" was but a remote possibility.

Despite the educational work done up to this time by the American Society for the Control of Cancer, official health agencies, and others, an aura of gloom and hopelessness clung to the disease, and, to many people, a diagnosis of cancer was equivalent to a deferred death sentence. Newspaper accounts of the deaths of cancer patients usually did not mention the cause of death. It was in this climate of thinking that the new Institute was launched.

The enormous problem to be solved and the uncertainties of the trail-blazing task assigned him were readily understood by Dr. Thomas Parran, then Surgeon General of the Public Health Service; but these facts did not daunt him. The new law was a directive from the Legislative Branch of the Government to lead an all-out attack on the cancer problem and

he accepted the challenge with courage. The task of organizing the new Institute and initiating its new programs was assigned to his able lieutenant, Dr. L. R. Thompson, Director of the National Institute of Health. Together they set themselves to the discharge of their new responsibilities with all the determination, enthusiasm, and resourcefulness at their command. To them, to the members of the first National Advisory Cancer Council, particularly Dr. Ludvig Hektoen, and to Dr. Carl Voegtlin, the Institute's first Chief, we pay tribute and express our deep appreciation and gratitude. Dr. Hektoen, at the age of seventy-four, resigned his position as chairman of the National Research Council to take a new one as member and executive director of the Council. Dr. Voegtlin had the difficult task of unifying and expanding the cancer research work of the Public Health Service to fit the dimension of the new legislation and at the same time equip and staff a new laboratory.

Twenty years have passed since these men undertook to meet the challenge handed to them by Congress. This seems to be an appropriate time for us to review their efforts and the developments that have taken place and to indicate the status of the Institute's work today.

Provisions of the National Cancer Institute Act

The National Cancer Institute Act established the Institute as a division of the Public Health Service. Section 2 of the law not only authorized, it *directed* the Surgeon General:

(a) To conduct, assist, and foster researches, investigations, experiments, and studies relating to the cause, prevention, and methods of diagnosis and treatment of cancer;
(b) To promote the coordination of researches conducted by the Institute and similar researches conducted by other agencies, organizations, and individuals;
(c) To procure, use, and lend radium [in accordance with provisions set forth in the law];
(d) To provide training and instruction in technical matters relating to the diagnosis and treatment of cancer;
(e) To provide fellowships in the Institute from funds appropriated or donated for such purpose;
(f) To secure for the Institute consultation services and advice of cancer experts from the United States and abroad; and
(g) To cooperate with State health agencies in the prevention, control, and eradication of cancer.

Some of these activities were entirely new to the Federal Government and, probably by way of smoothing the administrative pathway, the Congress more or less "spelled out" in detail, in other sections of the law, some of the actions the Surgeon General could take to put these directives into effect. For example, he was specifically authorized to make grants-in-aid for research projects recommended by the National Advisory Cancer Council and to provide the necessary facilities where training and instruction might be given in all technical matters relating to the diagnosis and treatment of cancer to such persons as he might designate. He was authorized to pay such persons a per diem allowance while in training and also to pay a stipend to research fellows.

In addition, the Surgeon General was authorized to adopt, upon recommendation of the National Advisory Cancer Council and with the approval of the Secretary of the Treasury, such other means of carrying out the purposes of the law as might seem appropriate or necessary in addition to those specifically mentioned in the law. The Council was specifically given authority to make such recommendations. Together, these two provisions gave the Council and the Surgeon General very wide latitude and showed that Congress wanted to reduce to a minimum the chance that the nation's cancer program would be handicapped as a result of their inability to foresee and provide specifically for all the contingencies that might arise.

The Act created a National Advisory Cancer Council of six members, besides the Surgeon General, *ex officio*, who was its chairman. All members were to be selected from leading medical or scientific authorities who were outstanding in the study, diagnosis, or treatment of cancer in the United States; they were to serve terms of three years, with the exception of the first six, two of whom were to be appointed for one-year terms and two for two-year terms, so that from the end of the first year there would be annual replacement of two members of the Council.

In brief, the law gave the Council the authority:

(a) To review research projects or programs submitted to it by others or initiated by its own members and to recommend to the Surgeon General any which it considered worthy of prosecution under the terms of the Act;

(b) To collect data regarding studies carried on in the United States or elsewhere relative to cancer, and to make this information available through appropriate publications;

(c) To review applications for grants-in-aid for cancer research projects and certify to the Surgeon General its approval of those which showed promise of making valuable contributions to knowledge with respect to cancer;

(d) To recommend the acceptance of conditional gifts offered to the Institute for cancer work.

The law authorized an appropriation of $750,000 for erecting and equipping a new building for the Institute and an annual appropriation of $700,000 for carrying out the program. In evaluating these appropriations today, one needs to bear in mind the difference between the purchasing power of the 1937 and 1957 dollar.

The Organization Period

In 1937 the country was still trying to pull itself out of a depression. This, added to the fact that the Government fiscal year was already well under way when the National Cancer Institute Act went into effect, undoubtedly influenced the decision of Congress to limit the Institute's first appropriation. Obviously, too, it would take time to activate the new programs if they were to be guided by well-thought-out policies. The amount granted was $400,000, and half of this was earmarked by Congress for the purchase of radium.

The first administrative step was, of course, the appointment of the National Advisory Cancer Council, since the Act provided that the pro-

gram should be carried out in cooperation with that body. These appointments were highly selective—every effort was made to secure men of vast knowledge and experience. No one could quarrel with the selections that were made; all were distinguished men of science. Dr. James Ewing and Dr. Frances Carter Wood were appointed for one-year terms, Dr. Ludvig Hektoen and Dr. C. C. Little for two-year terms, and Dr. Arthur Compton and Dr. James B. Conant for three-year terms. The able public health administrator, Dr. Thomas Parran, who as Surgeon General was the Council's chairman, provided it with dynamic administrative leadership. Dr. Hektoen was appointed executive director of the Council and in this capacity played a major role in the initiation of the Institute's extramural programs. It was his responsibility to carry on the Council's work between meetings and to serve as liaison officer between the Council and the Public Health Service.

A small administrative staff was assembled to assist in this work, in which other National Institute of Health personnel participated, all under the watchful eye of the Director of the Institute in whose office the Cancer Institute administrative unit was located. The National Institute of Health at that time was housed in buildings located in downtown Washington, but work was already under way on five new buildings at Bethesda, Maryland, on a tract of land donated to the Government for this purpose by Mr. and Mrs. Luke I. Wilson. When the National Cancer Institute Act was passed, Mrs. Wilson, whose husband had died in the interim, donated an additional tract of land for the sixth building, the new Cancer Institute. The land and these six buildings formed the nucleus for the large group of buildings which now house the seven Institutes and their 500-bed research hospital comprising the National Institutes of Health.

The first meeting of the Council was held on November 9, 1937, and was quickly followed by two others on November 27 and December 13. A fourth meeting was held on February 14, 1938. By this time the work on all the new programs was well under way. At the Council's first meeting it was decided that a conference of representatives of the most important organizations conducting or supporting cancer research would provide valuable information for all concerned and help in planning the new programs. The conference was held in Washington as part of the Council meeting on December 13, attended by representatives of the Jane Coffin Childs Memorial Fund and the Anna Fuller Fund, New Haven, Connecticut, the Rockefeller Institute for Medical Research and the Commonwealth Fund, New York City, the International Cancer Research Foundation, the American Oncologic Hospital, and the Lankenau Hospital Research Institute, Philadelphia, Pennsylvania, the Finney-Howell Research Foundation, Baltimore, Maryland, the Barnard Free Skin and Cancer Hospital, St. Louis, Missouri, the Chicago Tumor Institute, Chicago, Illinois, the State Institute for Malignant Diseases, Buffalo, New York, the Division of Biologic Sciences, University of Chicago, Chicago, Illinois, the Medical School of the University of Wisconsin,

Madison, Wisconsin, and the Medical School of Harvard University, Boston, Massachusetts, in addition to Council members and Public Health Service personnel.

The meeting was a very profitable one. The discussion dealt mainly with problems of cancer research, clinical cancer services, and cooperation among groups supporting cancer research. One immediate result was the appointment of a Committee on Fundamental Cancer Research ". . . to formulate, as far as this could be done, the fundamental aspects of the cancer problem and to suggest various lines of work which merit investigation." Committee members were Dr. James B. Murphy, Rockefeller Institute for Medical Research, chairman, Dr. Stanhope Bayne-Jones, dean of the School of Medicine, Yale University, Dr. Ross G. Harrison, chairman of the National Research Council, Dr. C. C. Little, director of the Roscoe B. Jackson Memorial Laboratory, and Dr. John Northrop, of the Rockefeller Institute for Medical Research. The Committee's report, a classic in its field, furnished the basic guidelines for fundamental cancer research. It was made available to the public through publication in the December 2, 1938, issue of *Public Health Reports* and is reproduced in full on page 317.

The New Programs

Perhaps each generation thinks that the years it has come through are the most trying and have caused the greatest upheaval and change of any period in history. Without stopping to argue this point, our own generation will agree that the twenty years from 1937 to 1957 have wrought great changes in the American scene. These changes are reflected in Government programs of all kinds, that of the National Cancer Institute among them. In looking back at the beginnings of the National Cancer Institute's new programs in 1937–38 it is important to remember that we are doing so from the vastly different vantage point of 1957.

Grants-in-Aid

Although a number of private agencies had supported research programs through a grant-in-aid system, no Federal Government agency had had authority to carry on such a program prior to the enactment of the National Cancer Institute Act. Accordingly, the National Advisory Cancer Council was deeply conscious of its responsibility in the inauguration of this new program. Not everyone was sold on the grant-in-aid system and at the first meeting of the Council the revered Ewing took advantage of the opportunity to express his opinion in these words: "I will get rid of a little feeling on this matter. I believe the whole policy of grants-in-aid is unsound. I wish to report after personally conversing with four or five of the best known men in charge of cancer research institutions in the world, that they regard it as the greatest handicap to their organizations' development." At the next meeting, Dr. Ewing submitted a prepared statement on the subject in which he recommended ways of remedying the defects in the grant-in-aid system.

No action was taken on applications for grants until the second meeting of the Council, when three of the twenty-eight applications received up to that time were recommended; two others were set aside for future consideration. At this meeting a policy to be followed in reviewing grant applications was adopted, one item of which is of special interest to us today as reflecting the basic philosophy underlying early Council actions. It read: "The Council, wishing to conserve the funds made available by Congress for the purpose of Cancer Research to the end that they may be employed to the best advantage of the country, and having in mind the somewhat unsatisfactory experience of bodies in connection with the too widespread awarding of small grants over a wide flung field, and further recognizing that many aspects of cancer research cannot be distinguished from research in pure biology, which may be outside the interest or responsibility of the Government—having in mind all these considerations, the Council RESOLVES that during the present fiscal year grants-in-aid will be made only in the case of projects closely connected with the work of the National Cancer Institute, with the exception of projects designed to improve the radiation therapy including the study of new methods of producing radioactive substances.

"The Council is agreed that fellowships with necessary stipends and allowances are highly important in developing first-rate men to study cancer, which is the great need of cancer research."

Only ten grants were recommended this first year, most of them for small amounts. The total funds granted were just under $91,000. In these days of atomic-weapon development and controversy over radioactive fallout, it is of interest to know that the largest single grant went to the University of California to support the work of Dr. E. O. Lawrence in developing the cyclotron for clinical research on therapeutic uses of neutron rays and artificial radioactive substances.

Research Fellowships

As was indicated by one paragraph of the Council's grant-in-aid policy quoted above, the members were keenly aware of the need to train more people in the techniques of cancer research. This awareness was even more keenly felt by the administrators of the Institute, who were faced with the problem of securing competent personnel to staff the expanding program. It was only natural, then, that during the first few years most of the research fellows appointed were assigned to the Institute or to work on grant-supported projects at other institutions in the hope that they might later be available for work at the Institute. These circumstances served to increase the care with which candidates were screened. That the policy followed and the judgment used in making appointments were sound is shown by the fact that several of the first research fellows appointed in 1938 and 1939 are members of the permanent staff of the National Cancer Institute today, one as associate director in charge of research. All of them, as well as staff members drawn from later research-fellowship appointments, have made

important contributions to our knowledge of cancer and have helped to formulate and guide the Institute's research program.

Training in Diagnosis and Treatment of Cancer

None of the new extramural programs authorized by the National Cancer Institute Act had greater appeal than the one concerned with medical training in the diagnosis and treatment of cancer. This, too, was a type of activity in which the Federal Government had not previously engaged.

It was generally conceded that much more could be done to control cancer if full use were made of the available knowledge concerning diagnosis and treatment. The problem was how to bring this about. The medical members of the Council, all of whom had been on medical teaching staffs, were well aware of the need to provide more and better training in cancer, and the opportunity provided under the new law was eagerly accepted.

On the medical side, the program planning was handled largely by a committee composed of Dr. Ewing, Dr. Hektoen, and Dr. Wood. Under the aegis of this committee a small group of representatives from medical schools and teaching hospitals held a conference at Memorial Hospital for the Treatment of Cancer and Allied Diseases in New York City early in January, 1938, at which there was a very free exchange of opinions. Information on the types of training available at leading cancer centers was secured. Special reports on training in diagnosis and treatment of cancer were prepared both by Dr. Wood and Dr. Ewing for the Council's use. Out of all this information the guiding principles for the program were formulated. Medical schools were advised of the plans for the program and the type of training that was thought desirable, and a list of suitable training centers was compiled.

The program took the form of training fellowships, later to be called "traineeships." Candidates were required to have completed at least a one-year internship following graduation from medical school, be acceptable to the training center to which they wished to go, indicate that it was their intention to devote themselves to a career in the field of cancer diagnosis and treatment, and have reasonable assurance of an opportunity to do so upon completing their training. The compensation was set at $6 per day, in line with the amounts then paid at Memorial Hospital, New York City, which was the leading training center. Each applicant was carefully screened by both personal interview and correspondence with his teachers and others. There were plenty of applicants from which to make selections, most of them having qualifications far in excess of the minimum requirement. By the end of the fiscal year, June 30, 1938, the program was a going one, with fourteen persons already, or about to be, appointed.

Radium Loan Program

The new authority "to purchase, . . . and lend radium" was one to be exercised with great caution. Not only was this a new program

for the Federal Government, it was one that had not been undertaken by any organization. The nearest approach to it was the rental of small amounts of radium by commercial concerns. The guidelines for the whole program had to be developed from scratch. The provision attached to the Institute's first appropriation, however, made it necessary to purchase $200,000 worth of radium before the end of June, 1938, if the funds were not to revert to the Treasury.

The Council was fortunate to have as a member the Nobel-Prize-winning physicist Dr. Arthur H. Compton, and both the Institute and the Council relied heavily upon him to provide basic information needed in determining the wisest course to pursue. Dr. Compton headed a committee which prepared a report on the status of cyclotrons then under construction or planned, since these instruments would produce a new type of radiation and new radioactive elements for use in cancer therapy. It was thought these developments might change the situation with regard to the use of radium. There was also the possibility that it might be best to buy radium for a large radium pack in order to determine once for all the merits of treatment with a 10 or 15 milligram radium pack. These and many other problems had to be considered before a final decision could be made, but ultimately it was decided that the money could be best used by purchasing radium in preparations of different sizes, to be lent to hospitals throughout the country for the treatment of cancer patients, plus a certain amount for research and treatment of patients at the clinical cancer research center then being developed at the U. S. Marine Hospital in Baltimore, Maryland.

The purchase amounted to approximately 9½ grams of radium in some 1600 units ranging from 1 to 25 milligrams and about 1 gram in solution to be used in a radon plant. The order was placed before the end of the fiscal year, but delivery of the radium and the necessary testing at the U. S. Bureau of Standards were not completed for another twelve months.

In the interim, many other administrative details had to be worked out, such as the type of shipping container necessary to protect persons and goods that might come in contact with the shipment, standards to be required of borrowing institutions for protection of their personnel, and standards of training to be required for radiologists using the Government radium for the treatment of patients. Last, but not least, a loan contract had to be formulated which would embody all the necessary conditions governing the loans.

The loan program did not actually get under way until the fall of 1939, two years after the Institute was established. By July, 1940, loans had been made to forty-seven hospitals.

Cancer Research

Studies of cancer had been under way in the Public Health Service for some fifteen years previous to the creation of the National Cancer Institute. The work had been conducted by two independent groups, one housed at Harvard University, Boston, and directed by Dr. J. W. Schereschewsky, and the other at the Hygienic Laboratory, predeces-

sor of the National Institutes of Health, in Washington. This group was attached to the Division of Pharmacology, under the direction of Dr. Carl Voegtlin. Upon the retirement of Dr. Schereschewsky, the Boston studies were placed under Dr. Voegtlin's direction.

A more extensive cancer research program and new laboratory facilities were made possible by the new legislation. The development of the expanded program was entrusted to the able hands of Dr. Voegtlin, who was appointed chief of the new Institute in January, 1938. Dr. Voegtlin brought to his new position a thorough scientific training and a knowledge gained from years of experience as a director and participant in laboratory research.

The already-existing Public Health Service cancer research staff of some ten or more well-trained investigators, each with five to fifteen years of cancer research experience, formed the nucleus of the new staff. This was gradually expanded, chiefly by the addition of research fellows, many of whom were to become permanent employees. New research studies were undertaken up to the limit of the available laboratory space, but full expansion of the program had to await the completion of the new National Cancer Institute building at Bethesda, Maryland. The newly issued report of the Committee on Fundamental Cancer Research, with which Dr. Voegtlin had served as an advisor, provided the guidelines for the expanded program.

Clinical Cancer Center

As part of its service to cancer patients who were beneficiaries of the Public Health Service and to provide a clinical cancer research center for the new Institute, the Public Health Service undertook, with Council approval, the development of a clinical cancer research center at the U. S. Marine Hospital in Baltimore. Dr. John E. Wirth was appointed director of this center, and a new 100-bed addition to the hospital, built to accommodate this clinic, was completed in the fall of 1939. Although the war prevented this clinic from ever reaching its full potential as a clinical research center, it provided facilities for a considerable program, especially when additional research funds became available in the interim between the close of the war and the completion of the Clinical Center at Bethesda. One of its important contributions, besides the excellent medical service provided to beneficiaries of the Public Health Service, was that it served as a center for the training of Public Health Service personnel in the diagnosis and treatment of cancer.

Cancer Control Activities

Very soon after the establishment of the new Institute, studies of cancer mortality and epidemiology were instituted by the States Relations Division of the Public Health Service, to which Institute funds were transferred for this purpose. There was great interest in the cancer problem among state health officials at this time and advisory services were provided to aid in state activities. A limited cancer education

program was also begun in cooperation with the American Society for the Control of Cancer.

Opening the New Building

Ground for the new Cancer Institute building was broken at appropriate ceremonies on October 3, 1938. A year later it was completed, and the staff at Boston, then under the administrative charge of Dr. Floyd C. Turner, was moved to Bethesda in October, 1939. By the end of January, 1940, all of the Cancer Institute personnel who had been located here and there had been moved to the new building. For the first time the cancer research work and all of the other cancer programs were brought together in one coordinated unit. The nation's cancer program was organized and ready to move forward.

1940–1947

For review purposes the history of the Institute from 1940 to the present time falls naturally into two periods: (1) July, 1940 to July, 1947—the years of national defense activities, the war years, and the postwar planning period; (2) July, 1947 to the present—the years of development and administration of the greatly expanded postwar program.

During the period 1940–47 the Institute's activities were under the direction of Dr. Carl Voegtlin, who served as its Chief until his retirement on July 31, 1943, and Dr. R. R. Spencer, who succeeded him and served until July 1, 1947. Under Dr. Voegtlin's guidance the several units brought together in the new National Cancer Institute building were integrated into an efficient and smoothly operated organization. The research program developed by him provided a sound foundation for the expansion which took place after World War II. Dr. Spencer, who had previously served as Assistant Chief, had the difficult task of guiding the Institute during the war years and of keeping its program going under severe handicaps. His interest and activities in the field of cancer education were an important stimulus to the development of a more extensive cancer educational program in the Institute. Two papers published in the *Journal of the National Cancer Institute* in 1940 and 1944 describe the organization and activities of the Institute in these respective periods and are of interest today for purposes of comparison.[2, 3]

The staff of the Institute averaged slightly over 100 persons during these years, but probably never exceeded 125, including scientific investigators, laboratory assistants, public health and administrative personnel. During the war period it was smaller than at any other time.

By the time the Institute's activities were fully organized in 1940, the effects of the war in Europe were being felt. In a report to the National

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[2] VOEGTLIN, CARL, and SPENCER, R. R.: The Federal cancer control program. J. Nat. Cancer Inst. 1:1-9, 1940.

[3] MARSHINO, ORA: Administration of the National Cancer Institute Act, August 5, 1937 to June 30, 1943. J. Nat. Cancer Inst. 4: 429-443, 1944.

Advisory Cancer Council in June of that year, Dr. Voegtlin, referring to the effect of the war on cancer research in Europe, said that he planned to make some changes in the Institute's program in order to curtail the number of long-term projects, on which time and money would be lost if they had to be discontinued before completion. In March, 1941, Dr. Voegtlin reported that he was having difficulty in keeping personnel, particularly laboratory assistants, because they were either being drafted or resigning to accept better-paying positions, which had become available as a result of defense activities. With the entry of the country into the war, the personnel problem became more acute. A number of the Institute's professional staff joined the Army or Navy or took positions in research work connected with the war effort. Many of the vacancies were filled by women—in one instance the wife of a scientist took his place in his absence. Women, both young and old, and older men were employed to fill the laboratory assistant jobs, and the suitability of older people for such work was demonstrated beyond doubt.

There was no great change in the amount of funds available for the Institute's work during this period. The budget for the fiscal year ending in June, 1940, was $570,000. Appropriations were continued at approximately this level, even through most of the war years, until 1945 when the amount was slightly less than $500,000. In 1944 the ceiling on the authorized appropriation for the Institute's work ($700,000) was removed when the new Public Health Service Act was passed. Most of the provisions of the National Cancer Institute Act were incorporated in this law, which codified and revised all previous Public Health Service legislation. In the first year after the war, the Institute's appropriation was increased to 1¾ millions, about three times the amount of any previous year.

Once initiated, all of the Institute's program went along at approximately the same level in terms of budget allotments. There were variations in the amounts spent for extramural programs, but these were due to the decrease in demand for the activity rather than to any change in availability of funds or administrative policy.

Trainees in Diagnosis and Treatment of Cancer

The needs of the Armed Services for medical personnel greatly reduced the number of physicians available for training in the diagnosis and treatment of cancer, and the number of persons serving under the traineeship program steadily decreased from 1942 until the war ended. Up to June 30, 1946, the total number of appointments was approximately ninety. With the return to civilian life of many young physicians and the increased appropriation in the fiscal year 1947, this program was greatly expanded.

Research Fellowships

Until after the end of the war, when additional funds became available, research-fellowship appointments were made mostly for the purpose of securing competent persons for the Institute's own staff.

Grants-in-Aid

Loss of personnel and shifts to war-connected research at the nation's research institutions retarded the development of cancer research and, consequently, there was a decrease rather than an increase in applications for grants-in-aid. In the fiscal year immediately preceding the end of the war, for example, only thirteen applications for grants were submitted to the National Advisory Cancer Council for review. The number probably would have been even smaller, had it not been for the work of the Council Subcommittee on Gastric Cancer, which worked hard to stimulate more research on cancer of the digestive system. (*See* p. 164.)

In 1945 the Council inaugurated a policy of recommending support of some grant-aided projects for periods longer than one year. Some investigators had indicated a reluctance to undertake cancer research because of limited opportunities for a continuing career in that field. The Council thought that a policy that assured continued support of a project in appropriate cases would be an incentive to more investigators to undertake cancer studies, especially those of a type that could not be completed in a short period of time.

Radium Loans

During the war a few institutions that had received radium loans from the Institute found it necessary to terminate them because of loss of personnel trained in radiology. However, there were always applications pending, and the total number of loans in effect during these years remained approximately the same.

One of the results of the radium loan program during this period was a better evaluation of methods of protecting personnel from overexposure to radiation. As part of the loan program, a survey was made in 1940 of the procedures used in handling and storing the radium in the borrowing hospitals. It was found in many hospitals that there was inadequate protection against overexposure to radiation of staff members handling the radium or working in rooms where it was stored. The data and the recommendations which resulted from the survey were of value not only to the hospitals concerned but also to all institutions and industries in which radioactive substances are used. As a result of the survey findings, the Advisory Committee on X-ray and Radium Protection changed its recommendation on the tolerance dose to a lower figure.[4]

Research

Despite the difficulties which were encountered almost as soon as the Institute's organization was completed, the staff continued to be enthusiastic and productive and made their due share of contributions to cancer knowledge. The research program so wisely planned by Dr. Voegtlin, when the Institute was first established, continued to reflect his judgment throughout the years. As the years went by and the pro-

[4] Cowie, Dean, and Scheele, Leonard A.: A survey of radiation protection in hospitals. J. Nat. Cancer Inst. 1: 767–787, 1941.

gram developed, a different type of organization appeared to be necessary for the best administration of the work. Accordingly in 1946, the staff was organized into six sections—biology, biochemistry, biophysics, chemotherapy, pathology, and endocrinology, each with a chairman. Most members of the research staff were affiliated with one of these sections, although there were still a few directly under the Chief of the Institute.

During the war the Institute undertook a number of studies that were related to the war effort and at the same time had a bearing on cancer. Notable among these were studies on the effects of radiation which were related to the development of the atomic bomb. They were conducted in cooperation with, and partly financed by, the Argonne National Laboratory at the University of Chicago. The Institute also released its director of clinical cancer research at the U. S. Marine Hospital in Baltimore to help in other research work on the atomic-bomb project conducted at Oak Ridge, Tennessee.

In addition to the knowledge that accrued from the Institute's research during the war, probably its most important contribution to the cancer program, not only in the United States but also throughout the world, was that it kept the work alive and going. Although the Institute's program had to be modified to fit changed conditions, it still maintained most of its activities at a rather high level. The National Advisory Cancer Council, in turn, continued to stimulate and recommend support for research in other institutions. Accordingly, when the war ended, research and other programs were still going, and the Institute and many other cancer centers were ready and waiting to go forward with the greatly expanded program that followed. This was a decided improvement over the situation in World War I, during which cancer research was so greatly disrupted that a long period was required to get it organized again.

An interesting account of the nature and accomplishments of the research program in these early years is contained in a paper entitled "Research Activities of the National Cancer Institute," by Dr. Michael B. Shimkin, published in the *Journal of the National Cancer Institute*, October, 1944.

Cancer Control Activities

From 1940 to July, 1946, the Institute continued to render advisory and other types of service to the state departments of health, to the extent possible with its limited staff. In July, 1946, funds for allotments to the states for cancer control activities were made available from the appropriation for the States Relations Division of the Public Health Service, a director of Cancer Control Activities was appointed in that Division, and the development of an expanded program was begun. A number of medical officers were given orientation and training in cancer control activities and assigned as consultants to the seven district offices of the Public Health Service.

A report on Cancer Services and Facilities prepared by the National

Advisory Cancer Council (*see* p. 164) was of special value in the development of the state programs. It outlined in detail the basic elements of a state cancer control program and presented pertinent cancer statistics and information on facilities and services for each state. It was made generally available through publication in the *Journal of the National Cancer Institute*, and copies were furnished to state health departments and other agencies concerned.

Limitations of staff and other circumstances prevented the Institute from sponsoring an extensive program of cancer education during this period. However, a small program was carried on through the distribution of literature, posters, films, and informal talks. The needs in this area were well known and the plans for meeting them formed the basis for the expanded program developed after the war. In 1944 the Chief of the Institute was awarded the Clement Cleveland Medal for his own contributions in the field of cancer health education.

In 1945 the Institute published its first pamphlet on cancer of a specific site, an educational folder on cancer of the breast. It was widely distributed by both the Institute and the American Cancer Society, which reproduced the folder for its own use. This pamphlet was the forerunner of a series of cancer-site pamphlets, which in later years were prepared jointly by the Institute and the Society.

Publications

The need for a journal in which to publish the reports of the Institute's work was soon apparent, and, after securing the necessary Budget Bureau approval, publication of the *Journal of the National Cancer Institute* was begun on a bimonthly basis in August, 1940. This *Journal* was to serve the twofold purpose of providing (1) prompt publication of reports of the work of the National Cancer Institute staff and (2) additional space for the publication of the work of outside investigators. The only journal devoted to the subject of cancer then in existence was the *American Journal of Cancer*, which ceased publication a few months later and was replaced by *Cancer Research*. The need for the *Journal* as an outlet for the Institute's own reports was well demonstrated by the six issues of volume 1. One of the six issues was devoted exclusively to the proceedings of the first National Conference on Gastric Cancer held under the auspices of the National Advisory Cancer Council. In the other five issues there were only three papers of which the Institute's staff were not either authors or coauthors. Among the papers from outside authors appearing in this first volume, perhaps the one of greatest historical interest is that of Dr. Leo Loeb, entitled "The Significance of Hormones in the Origin of Cancer."

Although a very large proportion of the papers issued from the Institute in the 1940–47 period were published in the *Journal*, there were many others that were published in appropriate outside journals. In addition, there were several publications issued as separate reports, monographs, or pamphlets, and as occasion arose an entire issue of the *Journal* was given

over to the publication of a special report or the proceedings of a conference.

Among the separate reports issued were a number on cancer statistics and epidemiology. Notable among these was the report on cancer incidence in ten cities located in various sections of the country. Separate reports were published on each city, followed by a consolidated report of the entire study. All but one of these were completed and published in 1940 or later. Two important monographs prepared by Institute staff members were "A Survey of Compounds That Have Been Tested for Carcinogenic Activity," by Dr. Jonathan Hartwell, published in 1941, and "A Symposium on Mammary Tumors in Mice," prepared by ten members of the staff. The latter was published by the American Association for the Advancement of Science in 1945, because the Institute's printing allowance at that time was not large enough to permit such an expenditure.

Each of these publications, and similar ones issued in later years, brought together in one volume the data or references then available on a selected subject, thus making the information easily accessible to researchers everywhere. They illustrate the types of service which large and well-financed institutions are best prepared to render and which result in immense savings of time, energy, and money to other institutions and individuals throughout the world.

The National Advisory Cancer Council

When Dr. Ludvig Hektoen, one of the first members of the National Advisory Cancer Council, completed his two-year term in 1939, he agreed to continue to serve on the Council in the capacity of executive director. He continued in this position until mid-1944, when he resigned and was succeeded by Dr. George M. Smith, of Yale University, then a Council member, who held the position until early in 1947. He was succeeded by Dr. A. C. Ivy, of Northwestern University.

The Council was kept in close touch with developments in the Institute's activities through reports by the Chief of the Institute and the executive director of the Council, the latter being especially concerned with developments and progress in extramural research aided by grants recommended by the Council. In addition to his own reports, the Chief of the Institute frequently had members of the staff report at Council meetings on special undertakings and progress in laboratory studies. Special efforts were made to have the Council members visit the laboratories for personal observation of the work.

After the Institute's new programs were organized and under way, the Council was able to devote more time to other phases of its work. Ways and means of promoting the nation's cancer program were discussed at meetings, and committees were appointed or individual members asked to secure information and make reports for the benefit of the entire Council. Among the more important committees active during the 1940–47 period was one on Cooperation in Cancer Research, which was established largely as a result of discussions led by Dr. James B. Murphy, and of which Dr. George M. Smith served as chairman.

On the recommendation of this Committee a program was initiated to exchange information between the Institute and other institutions making grants for research, with the objective of coordinating activities and avoiding duplication of effort. This Committee also took the lead in stimulating the initiation of research projects directed at the solution of specific problems on which it was thought desirable to concentrate. Out of this new approach grew the decision to make a special attack on gastrointestinal cancer, which accounted for a very large proportion of cancer deaths and on which little research was being done. A Subcommittee on Gastric Cancer was appointed early in 1940, and on its recommendation a conference on gastric cancer was held at the National Cancer Institute on October 11 and 12, 1940; about sixty people attended in addition to Institute and other Public Health Service personnel. As a result of this conference and the work of individual Council members, a large number of gastric-cancer studies were undertaken by groups of investigators at several institutions.

During the war, a second, much smaller conference on gastric cancer, attended chiefly by persons from cities near New York with three from Chicago and one from Cincinnati, was held at the Memorial Hospital for the Treatment of Cancer and Allied Diseases in New York City, November 11, 1944. The year after the war ended, the third conference was held at the University of Chicago, December 5 and 6, 1946.

In 1944, with hopes rising for the early termination of the war, the attention of the Council was turned to the need for postwar planning, and at the last meeting held that year the Surgeon General appointed a committee composed of Dr. George M. Smith, Dr. Frank E. Adair, and Dr. Sherwood Moore to study and report upon a number of activities related to: (1) the education of physicians in cancer diagnosis and treatment and (2) the organization of cancer services in the states.

The committee's report and recommendations, based on an extensive study, were approved by the Council and published in the April, 1946, issue of the *Journal of the National Cancer Institute*, which was devoted entirely to this subject. In brief, the committee said that its studies showed a need for medical schools to give more comprehensive and better-integrated courses in cancer and that there was an insufficient number of centers prepared to give postgraduate training to physicians in cancer pathology, cancer surgery, and cancer radiology. It was recommended that a conference be held with representatives responsible for planning cancer courses in the curriculums of medical schools with a view to developing improved methods of teaching cancer.

It was also recommended that the traineeship program of the Institute be expanded through the development of a larger number of training centers and an increase in the number of traineeships and that the Institute should assist in the development of long- and short-term postgraduate courses in cancer.

The committee said also that greater effort should be made to expand cancer research and to increase the use of available knowledge in con-

trolling cancer. It recommended that the Institute expand its programs of intramural research, research fellowships, and grants to support extramural research. Attention was directed to the fact that although methods of effecting a complete cancer service might vary in different states, the basic elements of a cancer program were essentially the same everywhere. It was recommended that the Institute assist state health departments in the development of adequate programs and that close cooperation be maintained between the Institute and voluntary agencies in the further development of cancer control activities in the United States.

Finally, the committee recommended that the Institute request appropriations sufficient to carry out the committee's recommendations.

The conference of representatives responsible for the planning of instruction in schools of medicine, recommended by the committee, was held at the National Cancer Institute in November, 1946. Out of this conference came a Council recommendation that the Public Health Service should consider ways and means of providing necessary financial assistance to interested medical schools prepared to undertake an integrated program of cancer teaching and that it should also try to interest other agencies in giving financial support to such a program. A subsidy of approximately $10,000 to $25,000 annually for a period of years was suggested. The report of this conference was published in the August, 1947, issue of the *Journal of the National Cancer Institute*.

The plans for the National Cancer Institute's postwar program were based largely on the Council's recommendations, contained in the reports mentioned. The Institute requested an increased appropriation for the fiscal year 1947. This was granted in the amount of 1.8 millions, more than three times the amount of any previous appropriation. In that year the Institute expanded its intramural research, allotted nearly half a million for grants to support extramural research, appointed fifty-nine new trainees, and expanded the research-fellowship program.

1947–1957

The program of the National Cancer Institute during the 10-year period ending July 1, 1957 has been an extensive and continually expanding one. Within the limitations of this report it is possible to touch only very briefly on the major changes and developments in programs and administration.

That the Institute would request a further increase in the size of its appropriations was foreshadowed by the recommendations of the National Advisory Cancer Council for new undertakings and expansion of existing programs. Such a request was submitted for 1947–48. Its favorable reception by the Bureau of the Budget, the discussion at the hearings before the Appropriations Committees, and other congressional actions

indicated that Congress would direct that the nation's cancer program be expanded.

With this possibility in view, the National Advisory Cancer Council recommended, and the Surgeon General appointed, a special committee of Council members and others to advise on the organization of the expanded program. The committee's report was presented to the Council for consideration in June, 1947, and, with the attendant discussion and recommendations it brought forth, the report was available later to assist the Institute administrators in planning and organizing the expanded program made possible by the appropriation of 14.5 millions. The appropriation act specifically stated that the funds could be used for grants for training projects and for the erection of buildings and the acquisition of lands therefor, an authority which the Institute had not previously had. The act also stated that the funds were to be used for grants to state health agencies.

New Organization

On July 1, 1947, Dr. Leonard A. Scheele became Director of the Institute and held this position until he was appointed Surgeon General in April, 1948. He was succeeded in May, 1948, by Dr. J. R. Heller, the present Director.

Up to July, 1947, the Institute had operated as a single unit under the direction of the Office of the Chief. The initiation of the greatly expanded program called for a new type of organization. Dr. Scheele had the important task, begun while he was the Institute's assistant chief, of effecting the reorganization necessary to administer the expanded postwar program. The Institute was reorganized into three branches dealing, respectively, with intramural cancer research, cancer research grants, and cancer control activities, each with its own administrative head.

Dr. Harry Eagle was appointed the first head of the newly created Research Branch and held this position until early 1949. Following the establishment of the Branch, the previous, informal arrangement of the research staff into sections with section chairmen became a formal arrangement. Sections were organized according to scientific disciplines and all research studies were grouped in the appropriate section. The following members of the staff, who had previously served as section chairmen, were designated as heads of the six sections in Bethesda: Dr. H. B. Andervont, Biology Section; Dr. Jesse P. Greenstein, Biochemistry Section; Dr. Egon Lorenz, Biophysics Section; Dr. Murray J. Shear, Chemotherapy Section; Dr. Roy Hertz, Endocrinology Section; and Dr. Harold L. Stewart, Pathology Section. Dr. Michael B. Shimkin headed the seventh section, the Laboratory of Experimental Oncology, in San Francisco. In 1952, Dr. G. Burroughs Mider, a former National Cancer Institute Research Fellow, was appointed Associate Director in Charge of Research, a position which he still holds.

The new Research Grants Branch, with a small staff, was headed by

Dr. David E. Price. He was succeeded, in 1948, by Dr. Ralph G. Meader, who still directs this Branch, now much larger.

Dr. Austin V. Deibert, who had directed the state cancer control activities of the States Relations Division of the Public Health Service in 1946–47, was transferred to the Institute to head the new Cancer Control Branch, which in turn was divided into a number of sections headed by chiefs responsible for developing and administering the various activities. Upon Dr. Deibert's transfer to another bureau of the Public Health Service, Dr. R. F. Kaiser, who had been assistant chief of the Branch, succeeded him in January, 1951, and has continued to serve in this capacity up to the present time.

In 1947 the Institute had to meet its needs for clinical research facilities by establishing clinical research studies in other institutions, because such facilities were not yet available at the Bethesda center. A new clinical research program was set up at that time in San Francisco, California, in cooperation with the University of California Medical School, under the direction of Dr. Michael B. Shimkin. The Cancer Clinic, directed by Dr. John E. Wirth, at the U. S. Marine Hospital in Baltimore, provided facilities for some additional clinical research studies, and a third group of studies was developed by Dr. Roy Hertz in cooperation with the George Washington University Medical School in Washington, D. C. These extramural clinical research programs were discontinued soon after the new clinical research hospital was opened in 1953 on the grounds of the National Institutes of Health. The Institute then established Branches of Medicine, Surgery, and Radiology to conduct clinical cancer studies, and, in 1954, Dr. Charles G. Zubrod was appointed Clinical Director of these studies.

Appropriations

As shown in the table below, the appropriations for the Institute from the fiscal year 1948 to the present have ranged from 14.5 millions in 1948 to 24.8 millions in 1956, and nearly double that amount—48.4 millions—for the fiscal year 1957. Congress specifically stated that 10 millions of the increase granted for the last year should be used for the chemotherapy program. This amount was in addition to an increase provided for this purpose in the Institute's requested budget, so that altogether about 19 millions of the total appropriation were allocated to the chemotherapy program.

Fiscal year	Appropriation
1948	$14, 500, 000
1949	14, 000, 000
1950	18, 900, 000
1951	20, 686, 000
1952	19, 500, 000
1953	17, 887, 000
1954	20, 237, 000
1955	21, 737, 000
1956	24, 828, 000
1957	48, 432, 000

These figures represent the actual amounts appropriated in the annual appropriation acts, and do not include any supplemental amounts that may have been granted for some special item, such as increased salaries granted by Congress for all Civil Service employees or some other specific expenditure. Such items, however, have little effect on the total funds available in any particular year.

There is usually a small gap between appropriations and expenditures, and in one or two years, the difference has been considerable. This is due to several factors, such as the practice of setting up reserves in the over-all Government budget in order to bring expenditures within certain limits; the Institute's inability, within the period covered by the appropriation, to develop, either with grantees or contractors, all of the work involved in one of the extramural programs; or inability to secure, within this same period, the trained personnel needed to carry on projects conducted directly by the Institute. In the current fiscal year, for example, for which the authorized appropriation is almost double that of the previous year, thus calling for a very rapid expansion of certain activities, not all of the funds will be spent.

Programs

The last ten years have witnessed not only great expansion of all of the Institute's already existing programs, with the exception of the radium loans, but also the initiation of many new ones, such as grants to state health departments to support state cancer control programs, grants to medical, dental, and osteopathic schools to support training in the diagnosis and treatment of cancer, grants for the construction of cancer research facilities, and grants to support field investigations. A Nursing Section has been established to promote nurse education in cancer, and a Cancer Reports Section created to promote cancer education activities through all available media and to keep the public adequately informed of the Institute's work. Many new field studies have been conducted by the Institute, and studies of statistical and epidemiologic data have been accelerated. As previously mentioned, developments in the field of chemotherapy have made it necessary to set up a special administrative group to handle the extramural activities that are a part of the expanded chemotherapy program.

Grant-Supported Programs

A very large part of the money that Congress has appropriated for the National Cancer Institute has been spent in the form of grants to support extramural programs conducted by institutions and agencies throughout the United States and as stipends to persons training for work in cancer. During this period a relatively small amount has also been granted to institutions in foreign countries for research projects or field investigations, which some circumstance made it desirable to undertake in these countries, such as the unique qualifications of the investigator or the availability of particular research material or epidemiologic data.

Table 1 shows the amounts that have been granted from 1948 through 1956 for the three new extramural programs begun in 1948 (undergraduate professional education, field investigations and demonstrations, and state cancer control programs) and for extramural cancer research projects from the date of establishment of the Institute through 1956. The total amount exceeds 96 millions. An additional amount has been granted for construction of research facilities (*see* section on Construction of Cancer Research Facilities, p. 176). Final data on grants made in the fiscal year 1957 will not be available in time to include in this report.

Undergraduate Professional Education

Professional education in approved medical, dental, and osteopathic schools has received support in the amount of 18.6 millions through annual grants of $25,000 to four-year medical schools and $5,000 to two-year schools, $5,000 to dental schools, and, since 1952, $25,000 to schools of osteopathy. All of the approved medical, dental, and osteopathic schools in the United States have participated in this program during most of the period under review. Text-figure 1 shows the number and location of the schools receiving cancer teaching grants in the current fiscal year.

Field Investigations and Demonstrations

In the program of grant-aided field investigations and demonstrations 9.4 millions have been awarded to agencies and institutions to support in full, or in part, field investigations, applied and developmental research, community studies, surveys, and pilot projects. All of these projects are designed to acquire information that will aid in more effective and widespread use of our present knowledge of cancer control, in the development of new diagnostic and case-finding techniques and methods for their mass application, and in the provision of adequate services and facilities for cancer diagnosis and treatment. Text-figure 2 shows the geographic distribution of these grants according to the states in which the grantees were located. Studies of special interest under this program are those concerned with the evaluation of diagnostic tests developed by various scientists in the last several years, efforts to develop other and more accurate tests, and further refinement, evaluation of accuracy, and determination of practicability of mass use of the cytologic technique for detection of cancer of accessible sites.

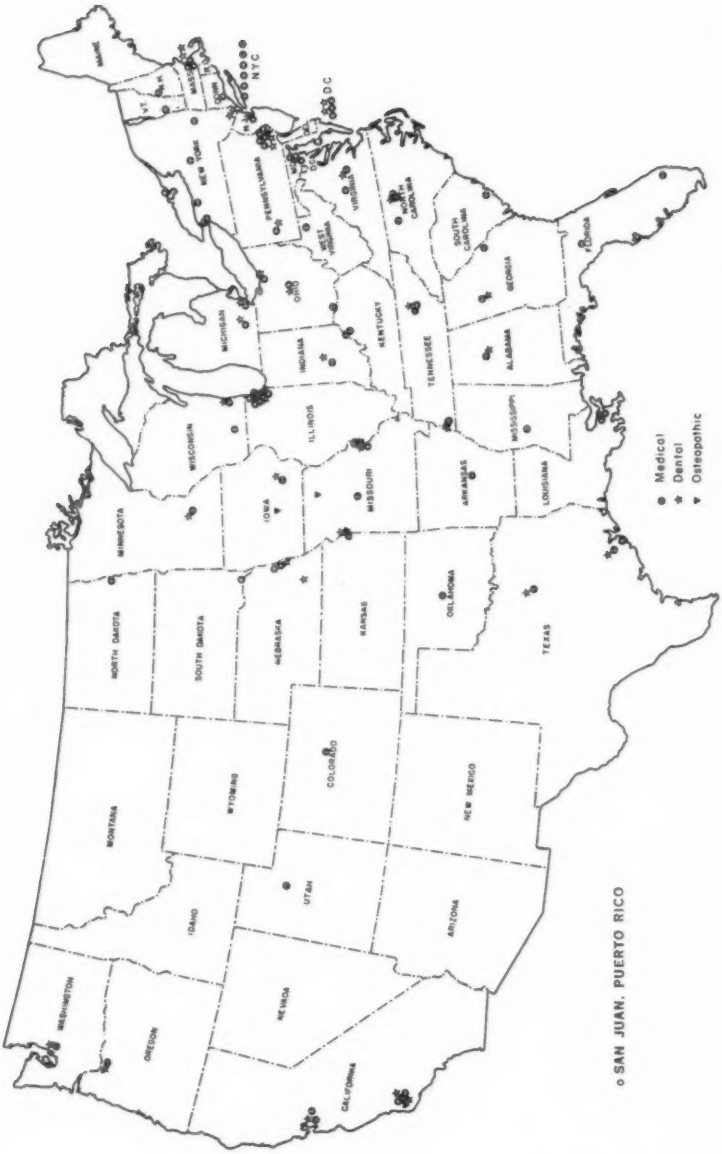
State Cancer Control Programs

The grants to support state cancer control programs conducted by state health departments amounted to 23.3 millions in the nine-year period. These funds are used to support cancer clinics, home-nursing care, follow-up services, limited laboratory services for indigent patients, statistical studies, and educational programs. The total annual grants to the states have ranged from 2.2 to 3.5 millions. This program is administered jointly by the Institute and the Bureau of State Services of the Public

TABLE 1.—*National Cancer Institute grants to support specified cancer activity, by state in which grantee was located*

State	Total	Grants to state health depts. to support state cancer control programs 1948–1956 fiscal years	Grants to medical, dental, and osteopathic schools to support education in cancer 1948–1956 fiscal years	Grants to support field investigations and demonstrations 1948–1956 fiscal years	Grants to support cancer research 1938–1956 fiscal years
Total	$96, 405, 130	$23, 255, 604	$18, 577, 939	$9, 391, 038	$45, 180, 549
Alabama	1, 362, 951	552, 849	234, 580	142, 817	432, 705
Alaska	38, 595	38, 595	—	—	—
Arizona	158, 411	104, 072	—	54, 339	—
Arkansas	766, 712	403, 419	223, 086	106, 010	34, 197
California	8, 494, 138	1, 397, 357	1, 377, 915	1, 084, 386	4, 634, 480
Colorado	879, 783	244, 299	225, 000	237, 752	172, 732
Connecticut	2, 065, 072	295, 527	229, 166	355, 464	1, 184, 915
Delaware	47, 187	47, 187	—	—	—
District of Columbia	2, 339, 142	118, 948	735, 166	339, 562	1, 145, 466
Florida	1, 123, 604	453, 349	74, 850	35, 300	560, 105
Georgia	1, 381, 504	613, 332	479, 140	95, 257	193, 775
Hawaii	132, 515	89, 621	—	42, 894	—
Idaho	159, 934	141, 777	—	2, 531	15, 626
Illinois	6, 006, 468	1, 304, 732	1, 268, 263	819, 270	2, 614, 203
Indiana	1, 143, 460	566, 035	200, 410	30, 000	347, 015
Iowa	1, 050, 990	438, 391	378, 460	23, 545	210, 594
Kansas	1, 046, 890	347, 523	225, 000	201, 207	273, 160
Kentucky	980, 448	577, 380	264, 249	52, 630	86, 189
Louisiana	1, 305, 220	466, 813	447, 633	64, 685	326, 089
Maine	1, 361, 561	172, 609	—	—	1, 188, 952
Maryland	2, 257, 640	327, 568	428, 719	203, 256	1, 298, 097
Massachusetts	8, 228, 566	782, 454	793, 159	490, 872	6, 162, 081
Michigan	2, 574, 220	858, 907	477, 055	197, 850	1, 040, 408
Minnesota	2, 009, 040	479, 683	264, 951	158, 979	1, 105, 427
Mississippi	591, 972	532, 262	59, 710	—	—
Missouri	2, 645, 319	555, 664	880, 810	207, 854	1, 000, 991
Montana	148, 865	111, 430	—	17, 966	19, 469
Nebraska	762, 175	184, 924	485, 493	21, 468	70, 290
Nevada	56, 419	56, 419	—	—	—

New Hampshire	40,000	—	40,000	—	—
New Jersey	981,933	659,392	—	91,725	230,816
New Mexico	185,402	125,191	—	—	60,211
New York	16,439,247	2,003,304	2,143,708	1,590,906	10,701,329
North Carolina	1,653,548	561,368	571,352	75,118	445,710
North Dakota	199,299	140,556	40,000	—	18,743
Ohio	3,207,521	1,176,959	708,040	214,541	1,107,981
Oklahoma	1,062,474	412,032	204,144	29,698	416,600
Oregon	872,500	191,624	252,966	58,883	369,027
Pennsylvania	6,594,871	1,357,691	1,438,111	572,541	3,226,528
Puerto Rico	630,564	314,150	129,166	127,440	59,808
Rhode Island	376,939	112,740	—	69,336	194,863
South Carolina	817,325	415,216	200,000	19,584	182,525
South Dakota	168,008	117,330	40,828	—	9,850
Tennessee	2,356,053	460,006	756,068	582,834	557,145
Texas	2,952,143	1,076,780	613,266	350,830	911,267
Utah	1,152,865	111,386	225,000	247,858	568,621
Vermont	533,678	93,079	214,383	63,531	162,685
Virginia	1,223,877	414,974	457,650	2,338	348,915
Virgin Islands	9,379	9,379	—	—	—
Washington	1,517,547	345,413	255,840	293,881	622,413
West Virginia	373,980	328,980	45,000	—	—
Wisconsin	1,830,511	478,463	489,602	—	862,446
Wyoming	106,665	86,465	—	14,100	6,100



TEXT-FIGURE 1.—Location of medical, dental, and osteopathic schools receiving cancer teaching grants, fiscal year 1957.

TEXT-FIGURE 2.—Total amount of National Cancer Institute funds granted to individuals and institutions to support field investigations and demonstrations, by state in which grantees were located, fiscal years 1948–56.

Health Service. The Institute transfers to the latter the necessary funds to cover the state grants and certain administrative costs within the Bureau. The basic principles of a state cancer program, as outlined by the National Advisory Cancer Council in its Report on Cancer Services and facilities in 1946, have served as guidelines for these programs.

More details on all of the preceding extramural programs are given in the report by Dr. R. F. Kaiser, page 259.

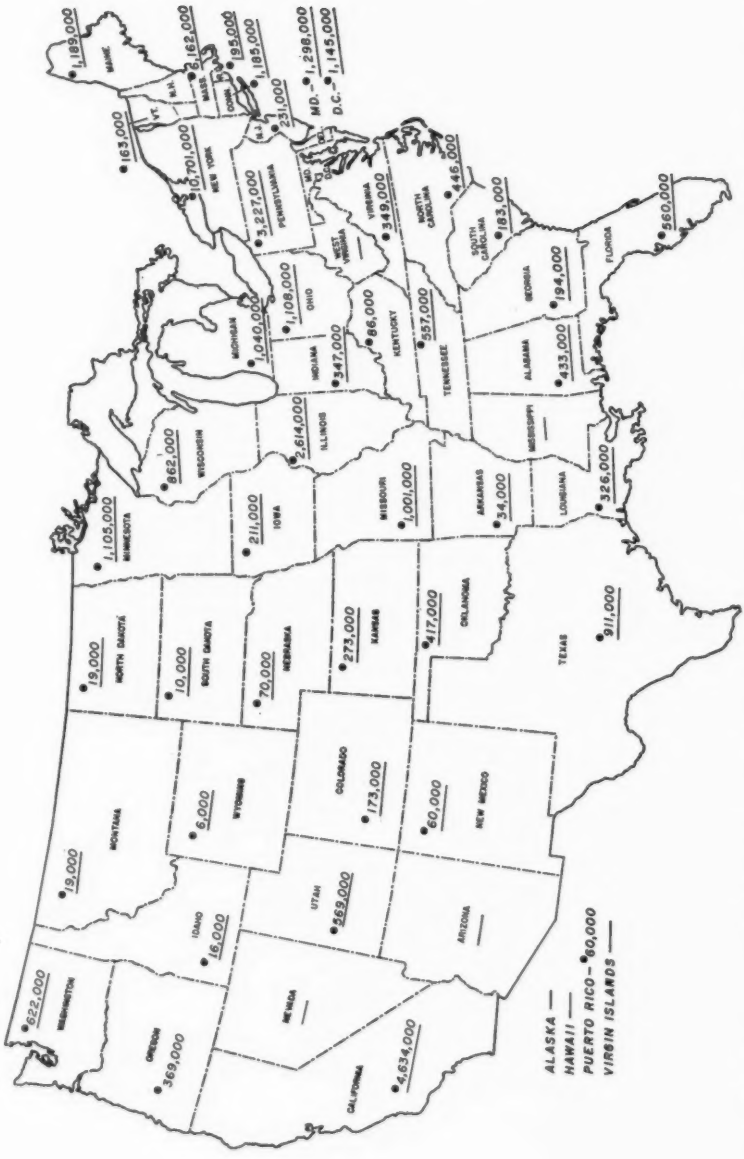
Extramural Research

The program of grants to finance cancer research in outside institutions has, of course, been the one most liberally supported, since it is through research that we hope to find the ultimate solutions to the cancer problem. Since the establishment of the Institute in 1937, 45.2 millions have been spent on this program, approximately 44 millions of this since July, 1947. In addition, $626,000 have been granted during the latter period to support cancer research projects conducted by investigators located at institutions in fifteen foreign countries, most of the money going to institutions in the British Isles, Canada, Denmark, France, and India. This program is discussed in greater detail in the paper by Dr. Ralph G. Meader on page 225.

The geographic distribution of these research grants, according to the states in which the grantees were located, is shown in text-figure 3. In a broad way this map indicates the availability of cancer research facilities and personnel in the respective states.

The expansion of research in cancer chemotherapy since 1953, under which large amounts of money have been allotted for support of extramural research, has made it necessary for the Institute to set up a special group to administer the extramural activities involved in this program. Accordingly, in 1955 the Cancer Chemotherapy National Service Center was established with Dr. Kenneth M. Endicott as administrative head. The grants awarded for support of extramural research in cancer chemotherapy are included in the 45.2 millions for support of all extramural cancer research, mentioned previously. The work of the Cancer Chemotherapy National Service Center is discussed in the paper by Dr. Endicott on page 275.

In administering its extramural grant programs, the Institute has the advice and guidance of the National Advisory Cancer Council, the Cancer Control Committee, and appropriate groups of scientists from among the twenty-seven study sections that function under the Research Grants Division of the National Institutes of Health. This Division, established as a very small service in 1946, has grown with the development of the National Institutes of Health and renders many administrative services on grant-in-aid programs to all the Institutes. The Cancer Institute pays its proportionate share of the costs of this service. All applications for grants to support cancer research projects are sent to this Division for referral to the study section that deals with the field of science represented by the proposed study. The project is then reviewed by a panel of



TEXT-FIGURE 3.—Total amount of National Cancer Institute funds granted to individuals and institutions to support cancer research projects, by states in which grantees were located, fiscal years 1938–56. (Figures rounded off to the nearest thousand.)

scientists, who evaluate the project and make recommendations which, in turn, are passed on to the National Advisory Cancer Council for its guidance in making final recommendation on the application.

The Division of Research Grants of the National Institutes of Health is also responsible for processing all grant payments and auditing grantees' accounts.

All applications for grants to support cancer teaching and field-investigation projects are referred, for preliminary study, to the Cancer Control Committee, which functions directly under the Institute. This Committee, made up of cancer clinicians, health officials, and teachers from medical schools and schools of public health, meets at an appropriate time before each meeting of the National Advisory Cancer Council, gives group consideration to the applications (which are sent to the members in advance), and makes its recommendations. The recommendations on each application are given to the Council members for their assistance in making a final evaluation of the proposed project.

Construction of Cancer Research Facilities

In addition to the above extramural programs supported by the Institute, another new grant-financed program, begun and completed during the last ten years, was that of expanding the nation's cancer research facilities. Funds for grants to construct cancer research facilities were made available in the 1948, 1949, and 1950 appropriation acts. Altogether 16.3 millions went into this program, which was administered by the Research Grants Branch of the Institute. These grants were awarded on the recommendation of the National Advisory Cancer Council. They supported construction of urgently needed clinical and laboratory facilities for cancer research at forty-nine non-Federal institutions in twenty-seven states and the District of Columbia, which were mostly medical schools and affiliated hospitals. In most cases the grants supplemented local funds.

Research Fellowships

Beginning with the fiscal year 1948 the amount allotted to the research-fellowship program has been gradually increased, and this year the figure stands at one million dollars.

Many new developments have taken place in this program in the last ten years, and today the program consists of several different elements. Briefly these are:

(1) Predoctoral, postdoctoral, and special research fellowships, each requiring different qualifications and carrying stipends that vary accordingly. From 1938 through the fiscal year 1956, 984 such research fellowships were awarded. This program is coordinated with the research fellowship program of all the Institutes of the National Institutes of Health. An over-all qualifications committee recommends

qualifications, policies, etc., to govern the program. A Cancer Specialty Board made up of Cancer Institute personnel selects the candidates for the cancer research-fellowship awards and the Division of Research Grants of the National Institutes of Health handles the administrative phases of the program.

(2) Awards to medical, dental, nursing, and public health schools of a number of $600 units, plus indirect costs. The school may award these units to undergraduate students for part-time cancer research work during the school year or full-time work at any period of the year when the student is not pursuing his regular curriculum. This program was initiated in the fiscal year 1956, which is the only one for which complete figures are available. The number of unit awards made in that year was 256, all but eight of which were to medical schools.

(3) In addition to these fellowships, the Institute this year has inaugurated another activity directed toward the same goal. This is a grant-in-aid program and consists of research training grants to institutions. The grants are used by the institution to finance the training of promising investigators in specified areas of cancer research; both the selection of the candidate and the amount of the stipend is left to the institution. Applications for these grants are submitted to the National Advisory Cancer Council for review and recommendation by the same procedure as that for applications for grants to support any other type of research or training project. The program is administered by the Institute's Research Grants Branch, with the usual assistance from the Division of Research Grants of the National Institutes of Health. The Institute has allotted 1.2 millions for the support of this program in the current year.

Traineeships

The program of postgraduate training for physicians in the diagnosis and treatment of cancer has made great strides in the last ten years. Previous to the fiscal year 1948 the total spent on this program was just under a half million. Beginning with that year more than 4.2 millions have been spent on this activity. This includes $730,000 allotted to this program in the current year. Part of this increase represents an increase in the stipend paid to trainees, the limitation on the amount as provided in the original National Cancer Institute Act having been removed by subsequent legislation. The stipend is now determined administratively and, at present, is $3,800 for an individual taking his first year of training, $4,200 for the second year, and $4,600 for the third year, with some additional allowances for dependents and necessary travel. These increased stipends are in line with increases in the cost of

living and also are designed as incentives to trainees to continue their training up to the maximum of three years. From the beginning of this program in 1938 to the present time, nearly 800 physicians have completed a course of training, which in practically all cases was of one to three years' duration. Approximately 160 are in training at this time.

It is probably fair to say that this program makes a greater immediate contribution to the welfare of the cancer patient than any other conducted by the Institute. Upon completion of their studies most of the trainees engage in work that is directly related to the patient. Many of them are diplomates in one of the specialties involved in the diagnosis and treatment of cancer. Most of them engage in private practice or serve on the staffs of hospitals and cancer clinics. A recent survey shows that at least one fifth of the physicians who have had these specialized courses are spending full or part time in teaching, thus extending the benefits of their own training to large numbers of other physicians.

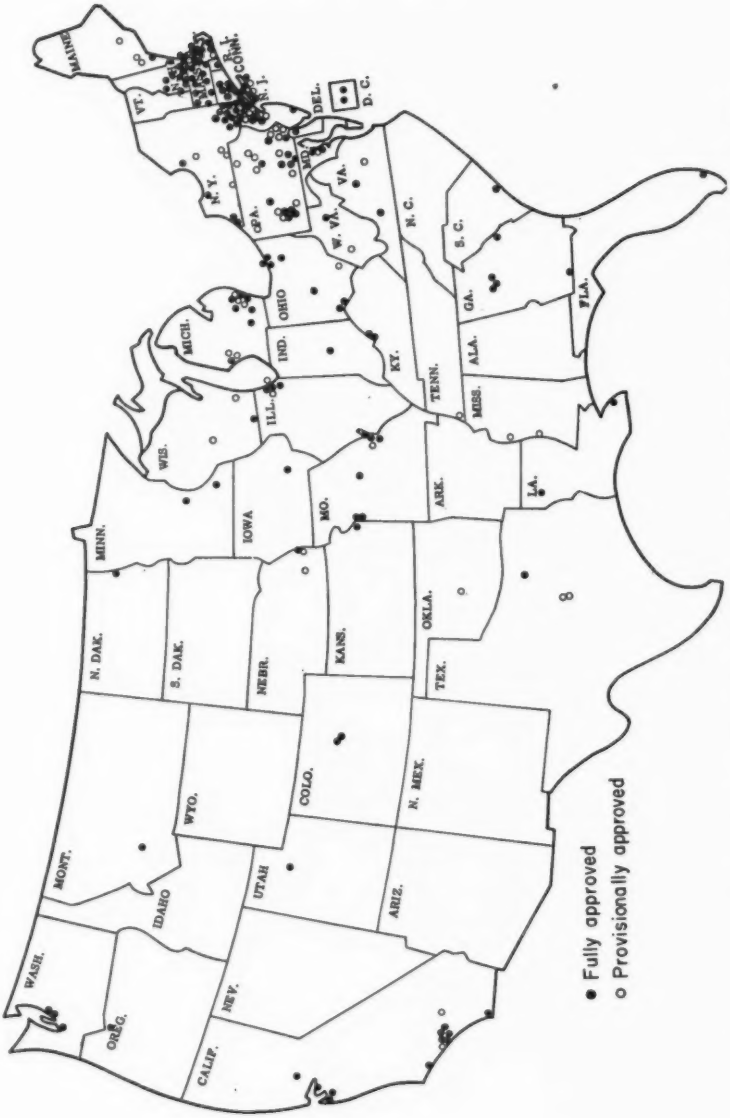
This program and the grant-aided state cancer control programs undoubtedly have been important factors in the expansion and improvement of cancer services and facilities throughout the country. Although many of the improvements in these services are difficult to measure, there is available tangible evidence of the expansion of specialized cancer services in the approval lists issued annually by the American College of Surgeons, which show a substantial increase, from 1937 to 1956, in the number of approved cancer diagnostic and treatment clinics and cancer diagnostic clinics in the United States (*see* text-figs. 4 and 5).

Intramural Programs

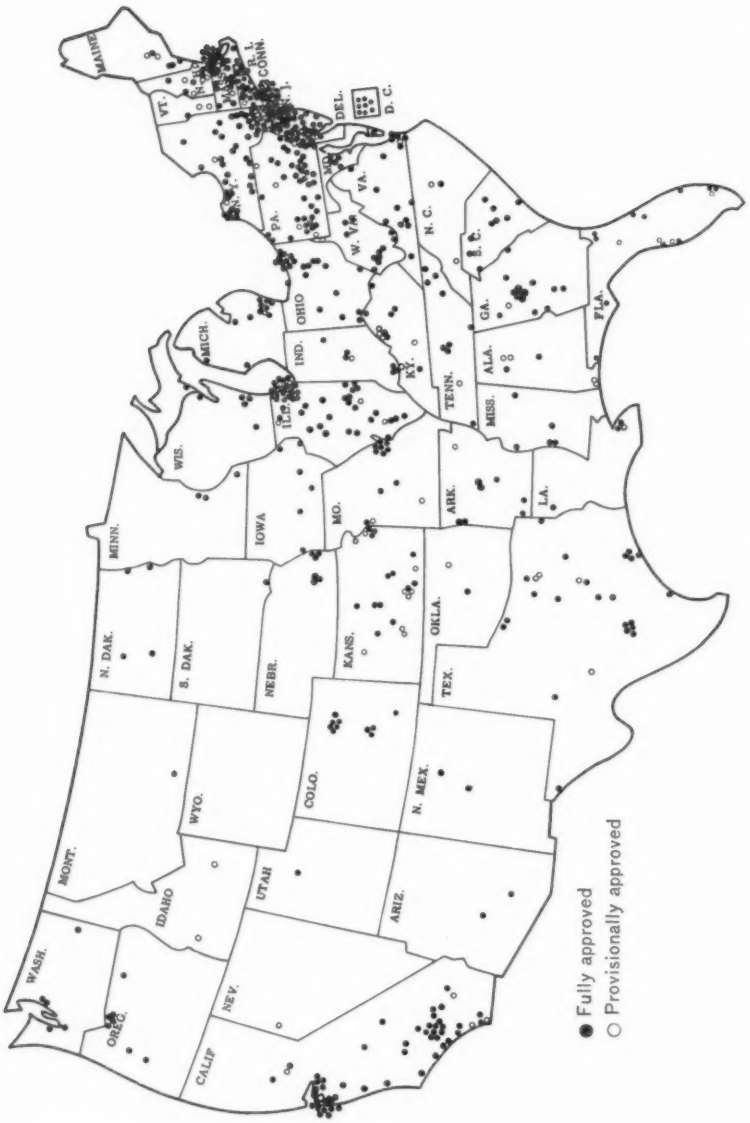
In general the term "intramural," as applied to the Institute's work, refers to those programs conducted by members of the Institute's own staff either at the Institute or in the field, as contrasted with programs supported by some type of Institute grant and conducted by outside agencies. In a few instances, notably certain field investigations and demonstrations, there may be participation by both the Institute's staff and a grant-aided group. Such joint endeavors promote efficient operation, since they make it possible for the Institute to have the services of well-trained people on the staff of an outside institution or agency and at the same time leave those staffs intact.

Research

The last ten years have witnessed great growth in the Institute's research program, with funds available for research increasing from 3.1 millions in 1948 to 8.0 millions in the current fiscal year. From six sections—biochemistry, biology, biophysics, chemotherapy, endocrinology, and pathology—and clinical research units operating at outside institutions, the research studies have been expanded and are now organized in 10 groups—five laboratories and five branches—the latter primarily concerned with the large clinical cancer research program in the new Clinical



TEXT-FIGURE 4.—Approved cancer diagnostic clinics and cancer diagnostic and treatment clinics, 1937.



TEXT-FIGURE 5.—Approved cancer diagnostic clinics and cancer diagnostic and treatment clinics—now designated as "cancer services"—1956

Center. These laboratories and branches are now divided into a number of sections, each under the direction of a responsible chief, and these in turn consist of several research units. The research staff now averages between 550 and 600 people, including clerks, technicians, animal caretakers, and other ancillary personnel.

The gradual activation of the Institute's allotment of research beds in the Clinical Center at Bethesda from 1953 to the present time has brought about many changes in activities, the inauguration of new studies, and many laboratory shifts. There have been delays, handicaps, and frustrations, which are the inevitable accompaniment to the opening of a new institution of the size of the Clinical Center and which tax the energies and patience of administrators and researchers alike. The progress made under these trying circumstances is evidence of the high quality of the staff.

In considering the increased funds spent for intramural research it is important to keep in mind that the 1948 figure (a big increase over the earlier years of the Institute) includes some funds for clinical services and maintenance of cancer patients at the centers where the Institute was then conducting its clinical research, and that the figure of 8.0 millions for the current year includes the Institute's proportionate share of the cost of operation of the Clinical Center of the National Institutes of Health. Establishment of this Center has, of course, made possible the inauguration of an extensive clinical cancer research program. The availability of clinical material may be gauged somewhat from the average daily census of cancer patients, which was sixty-eight in the fiscal year 1956, and from the weekly census in the current year which has ranged from sixty-eight to eighty-three patients. When the Clinical Center is operating at full capacity, the Institute will have about 140 beds available for cancer patients.

The Institute's research program is reviewed in the paper by Dr. G. Burroughs Mider, page 191.

Field Investigations, Demonstrations, and Statistical Studies

Previous to the expansion of the Institute's program in 1947–48, its field studies had been limited chiefly to the collection of epidemiologic data on cancer cases and controls, the incidence of cancer of selected sites, and the analysis of cancer-mortality statistics. With the beginning of the expanded program this phase of the Institute's work received great impetus, and more and more studies have been undertaken each year, some partially supported by field investigations grants. A number of studies have been completed and the results made available for the use of other agencies through appropriate publications. Many are still under way. Major efforts have been placed on studies of environmental cancer, efforts to determine the causes of cancer of specific sites, studies of diagnostic tests, investigations in the field of exfoliative cytology, and epidemiologic studies. In the epidemiologic and statistical studies, particular emphasis has been placed on cancer of the lung, uterus, and breast.

One of the very first studies initiated in the fiscal year 1948, under the expanded program, was concerned with the evaluation of cytodiagnosis, and this subject has been under constant study ever since. At the specific direction of Congress still greater emphasis has been placed on these studies in the last two years. In the increase in the appropriation granted the Institute for the current year, one million dollars was specifically earmarked by Congress for the purpose of broadening the cancer cytology services.

Data on cancer epidemiology gathered in earlier years have been analyzed and new studies in epidemiology undertaken. Many of these studies will require several years to complete.

The survey of cancer incidence in ten cities, referred to earlier in this report, was repeated ten years later in order to compare the data for the two periods. This survey is the largest of this type ever made and the data will be of continuing usefulness for comparative purposes.

Another important study of cancer incidence and survival rates was conducted jointly by the Institute and the Connecticut State Department of Health (Division of Cancer and Other Chronic Diseases) based on the data from the Connecticut cancer registry, which has been maintained since 1935. This study was supported in part by field investigations grants, and technical assistance was furnished directly by the Institute. The report, published by the Connecticut State Department of Health under the title *Cancer in Connecticut 1935–1951*, contains the most comprehensive data available in the United States on cancer survival rates.

A number of large-scale demonstrations have been carried out, usually on a cooperative basis by Institute and local staffs. For example, a statewide project was conducted in Iowa to evaluate the effectiveness of a particular educational tool in the control of breast cancer. Several demonstrations have been concerned with public health nursing activities in local cancer services.

Another phase of this program is consultation services to other agencies in planning their own studies and demonstrations.

Nurse Education Program

In recognition of the importance of the role of the nurse in the cancer control program, a Cancer Nursing Section was established by the Cancer Control Branch immediately after its organization in the fiscal year 1948, with Miss Rosalie Peterson in charge. Its purpose was to conduct an educational program directed toward improving clinical and public health nursing services for the cancer patient. The division works with nurse organizations, nurse educators, and public health nursing directors, supervisors, and consultants in an effort to improve education in cancer for both student nurses and those engaged in clinical or public health nursing work. Its staff conducts courses, studies, and demonstrations either alone or in cooperation with other agencies and plans projects that are carried out by other institutions with grant support. It also prepares cancer education materials for nurses and devises and validates

tests for activities concerned with nurse education or performance in relation to the needs of the cancer patient. A cancer nursing manual issued by the division in 1950 and revised in 1955 has been widely used in this country and has been translated into several foreign languages for use in other countries.

Radium Loans

The radium loan program, which required so much time and effort for its launching, is, by nature, subject to little change. The program has been continued as originally undertaken. Throughout this period the Institute has had the continued assistance of the National Bureau of Standards in testing the radium preparations as needed and in storing and caring for the radium between shipments to hospitals.

Education and Information Activities

The expansion of the Institute's cancer education and information activities has, of course, been a corollary of the development of its new programs and the expansion of old ones. This program was expanded immediately following the reorganization of the Institute in the fiscal year 1948 and a special Cancer Reports Section was set up to develop materials and render necessary services. It has functioned continuously since that time, with emphasis shifting as the needs changed.

Through reports, articles, review papers, radio programs, press releases, and other types of information materials and services to the press, the Institute has endeavored to keep the public informed of its activities and accomplishments. All of the usual types of educational materials, such as films, slides, posters, exhibits, and pamphlets are produced and made available for use by other organizations in carrying on cancer education work, and large numbers of public inquiries are answered individually.

Complete programs, frequently of a day's duration, are arranged for groups of visiting physicians and research scientists from all over the United States and foreign countries. Institute scientists also participate in the programs of medical and scientific organizations which hold meetings at the National Institutes of Health as a means of becoming familiar with the institution and its work.

As occasion arises, programs and materials are designed for use with special groups or in support of a particular project. Examples of such programs are the production of films on cancer of specific sites for use in educational work among practicing physicians; films and other materials prepared for use in an educational campaign among women on cancer of the breast; and a recent program carried out in high schools in cooperation with the National Science Teachers Association, designed with the twofold purpose of increasing the student's knowledge of cancer and interesting him in a career in scientific research.

Many of the Institute's films and educational pamphlets have been produced jointly with the American Cancer Society.

Publications

The reports of fundamental and clinical cancer research studies, as well as some of the reports of field studies conducted by the Institute, are published in the *Journal of the National Cancer Institute* and other appropriate scientific or public health journals. Frequently the nature of the study, the material to be published, or the intended distribution make it desirable to issue a separate publication.

Journal of the National Cancer Institute

The Journal of the National Cancer Institute was inaugurated in 1940 as a bimonthly publication and continued as such until July 1, 1956, when publication on a monthly basis was begun. One thousand free copies of each issue are printed, and all but a small reserve are distributed to institutions and scientists throughout the world. The *Journal* is sold by the Government Printing Office at a subscription rate of $20.00 per year in the United States, Canada, and Mexico, and $25.00 in foreign countries. The paid subscription list is usually between 600 and 700 copies. Through free and paid subscriptions, the *Journal* reaches forty-seven states, the District of Columbia, Hawaii, and Puerto Rico, and sixty-five foreign countries. In addition, copies are sent to each of the 353 Government depository libraries throughout the nation. Besides individuals, the subscription lists include research foundations, medical and scientific organizations, hospitals, medical schools, universities, drug companies, and libraries.

The *Journal* was established with the intention of providing an outlet for the papers of non-Institute investigators as well as for the Institute's staff, and this policy has been followed consistently. Occasionally, an entire issue of the *Journal* has been devoted to the publication of the proceedings of a special conference held under Institute auspices or to the publication of some special report, when this seemed to be appropriate.

Other Publications

Technical monographs, bibliographies, manuals, and other reference works also are published. Some of these, though vitally needed and of great service to scientists or public health workers, are expensive and beyond the means of any but large organizations and institutions.

Among the more important or widely used publications issued in the last ten years are: *An Index of Tumor Chemotherapy*, a new edition of *A Survey of Compounds That Have Been Tested for Carcinogenic Activity*, the *Cancer Nursing Manual*, the *Cancer Manual for Public Health Officers*, three editions of a directory and reference-type report, *Cancer Services and Facilities in the United States*, monographs on *Cancer Nursing in the Basic Professional Nursing Curriculum*, *A Methodology for Environmental and Occupational Cancer Surveys*, *Tobacco Smoking Patterns in the United States*, *A Quest into the Environmental Causes of Cancer of the Lung*, *Evaluation of Cancer Diagnostic Tests*, *Cancer Morbidity in Urban and Rural Iowa*, *Morbidity*

from Cancer in the United States (the report of the second cancer-incidence study in ten cities on which reports were also published for each city), and the *Bibliography of the Cytologic Diagnosis of Cancer*.

As previously mentioned, the Institute has also issued a number of publications in the field of cancer education.

The National Advisory Cancer Council

The National Advisory Cancer Council has also undergone some changes since 1947 as a result of legislation enacted in 1950. The new legislation provides that the Council shall be composed of twelve members, the Surgeon General of the Public Health Service, who is the chairman, the chief medical officer of the Veterans Administration or his representative, and a medical officer designated by the Secretary of Defense, who shall be *ex officio* members. The twelve appointed members must be leaders in the fields of fundamental and medical sciences or public affairs, and at least six must be selected from among leading medical or scientific authorities who are outstanding in the study, diagnosis, or treatment of cancer. The terms of the appointed members are now four years, instead of three years as formerly, and the terms are arranged so that three new members are appointed each year.

This new legislation also provided that the terms of the Council members then serving should expire as of September 30, 1950, but that service up to that date should not be considered as a "preceding term" that would prevent immediate reappointment. All members whose terms were cut short by the new legislation were reappointed.

Up to June 30, 1951, the Council had an officer, designated "executive director," who was usually an active or former member of the Council. At that time, the appointment of Dr. A. C. Ivy, who had held this position from July, 1947, expired. Inasmuch as the Institute, by that time, had a fully developed Research Grants Branch and a Cancer Control Branch, the staffs of which were available to assist the Council in its administrative duties, and since numerous services in connection with the review of applications for grants-in-aid were also available through the Division of Research Grants of the National Institutes of Health, it was deemed unnecessary to continue the position of executive director, and no successor to Dr. Ivy was appointed.

As indicated elsewhere in this report, the increase in appropriations for the Institute's work begun by Congress in the fiscal year 1948 has permitted the allocation of increasingly large amounts for grants to support cancer research and other grant-supported activities. With the availability of funds there has been a corresponding increase in the number of applications submitted for the Council's consideration. As a consequence, the Council's time and attention, of necessity, have been focused largely on problems related to grant-in-aid programs supported by the Institute. Throughout these years it has continually reviewed the merits and shortcomings of various methods of supporting research, *i.e.*, project grants, grants to individual investigators, grants to a group of investigators, or

institutional grants to be used to support specific projects. Planning committees have had to consider the many problems involved in any grant-in-aid program and the advantages or disadvantages of one method as compared with others. Out of this has come the conclusion that no one method will fit all cases and that the type of grant to be given must be determined by the circumstances in each case.

Corollary to evaluating methods of support has been the work of the Council in investigating and determining those areas in cancer research in need of stimulation and increased support. Several committees have worked on this problem and a number of conferences have been sponsored, usually in cooperation with other interested groups, on subjects such as cancer immunology, chemotherapy, radiation, etiology, and carcinogenesis. Such conferences provide the material needed for planning new attacks on the cancer problem in specific areas of research.

The Gastrointestinal Cancer Committee, formerly called Gastric Cancer Committee, has been continued and has sponsored three national conferences on gastrointestinal cancer during this period. Other active Council committees at present are those dealing with finance, planning, chemotherapy, and training grants.

Throughout the ten-year period the Council has been of great assistance to the Director and staff of the Institute in advising on policy matters affecting the Institute as a whole.

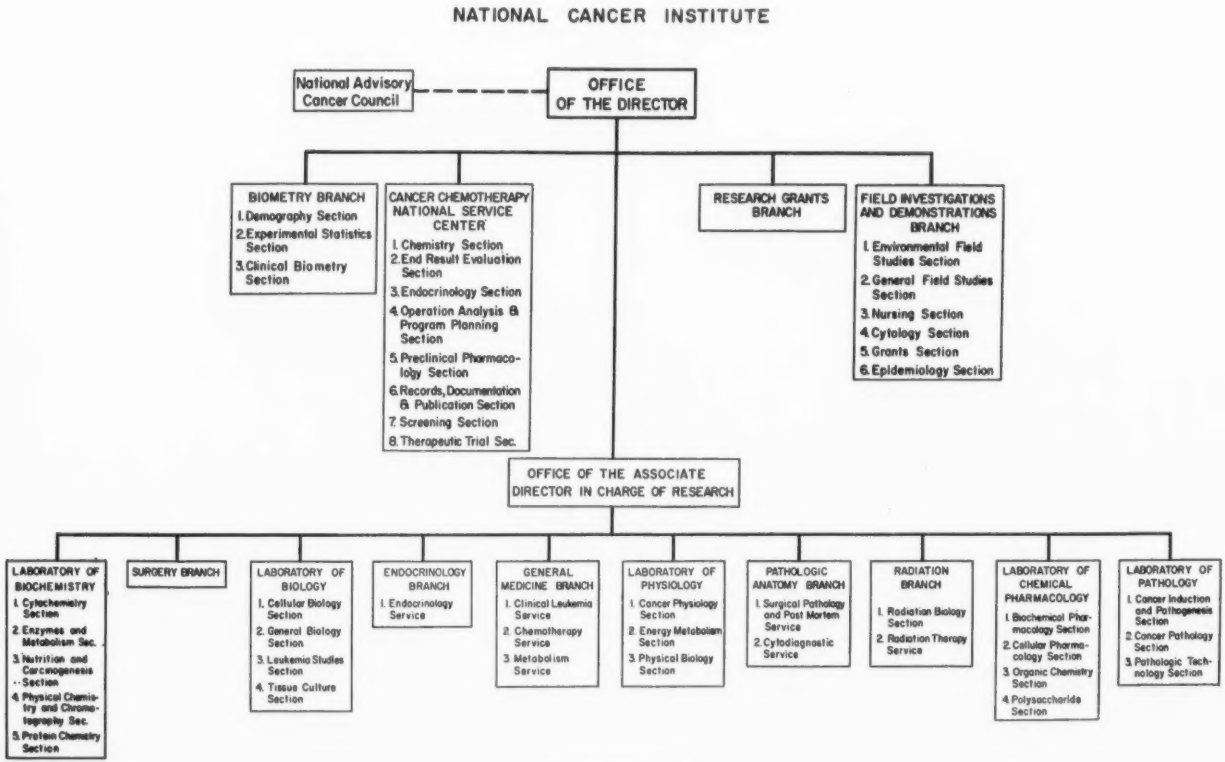
A list of present and former Council members will be found in the Appendix, on page 335.

The National Cancer Institute in 1957

In the fiscal year 1957, the twentieth year of its existence, the National Cancer Institute is operating with an appropriation of 48.4 million dollars as compared with $400,000 in its first year, 1938. About 32.7 million of this appropriation are allotted for grants to other agencies and individuals to finance research projects, research fellowships, undergraduate and postgraduate professional education in cancer, field investigations, and state cancer control programs.

For administrative purposes all the Institute's activities are grouped into six broad categories: administration, fundamental and clinical research, research grants and fellowships, cancer control activities (field investigations, demonstrations, and professional education), biometric studies, and the Cancer Chemotherapy National Service Center. A Cancer Reports Section attached to the Office of the Director carries on the public information and cancer education program. Text-figure 6, page 187, shows the Institute's organization.

Inasmuch as the appropriation granted for this year is nearly double that of the previous year, staff recruiting has been continuous in an effort to secure the number of trained people needed to carry on the expanded program. Inability to secure personnel has made it impossible to expand



TEXT-FIGURE 6

some of the activities as rapidly as desired and is one of the reasons not all of the funds appropriated will be spent. The staff, in May, numbered slightly more than 860, and the figure is expected to reach 1,000 by June 30. The names of all present staff members are given in the Appendix on page 339.

Over all, the three fields of study receiving the most emphasis are chemotherapy, diagnostic cytology, and environmental cancer, the first two at the specific direction of Congress. In the current year some 19 millions were allotted to finance the work of the Cancer Chemotherapy National Service Center, which is described in the paper on page 275. Approximately 2.2 millions were allotted to support work in cytology. Field studies, in which data will be assembled on a number of facets of cytology as a cancer diagnostic technique, are under way or in process of organization in twelve geographic areas of the country. In addition, a number of grant-supported cytology field studies are being conducted as well as intramural studies on this subject. Due to inability to expand the chemotherapy and cytology studies as rapidly as the funds permit, neither of these allotments will be entirely spent by the end of the year.

In the environmental cancer area, the Institute has a large number of direct and grant-supported field studies under way in addition to intramural laboratory studies. Leukemia, lung cancer in which there has been a dramatic rise in recent years, and the results of exposure to radioactive elements are receiving major attention in the field studies. The intramural laboratory studies include work on the cancer-producing properties of elements found in coal tar, petroleum and asphalt fumes, cutting oil fogs, coffee roast soot, chromite ore, and metallic nickel dust. Food additives and contaminants, macromolecular polymers, and plasma substitutes are also being studied.

The extent of the Institute's current program is indicated by the following:

Some 225 studies are being conducted in laboratory and clinical cancer at Bethesda, and approximately sixty field studies dealing with factors relating to cancer as it is found in the human population are under way.

Field studies supported in whole or in part by Institute grants total 109.

Cancer teaching courses are being supported at all approved medical schools, six approved osteopathic schools, and all but one approved dental school.

As of May 31, there were 161 physicians receiving specialized training in the diagnosis and treatment of cancer under the traineeship program. The number varies from month to month, but this year has never been lower than 146.

State health department cancer control programs are being supported with grants amounting to approximately 2.2 millions.

Grants paid this year to support research projects number over 1,100 and amount to more than 18 million dollars. Nearly 400 of these grants, amounting to more than 10.1 million, were for chemotherapy studies.

To help provide trained scientists, 140 predoctoral, 103 postdoctoral,

and 14 special fellowship awards were made this fiscal year; in addition, 128 awards of part-time fellowships were made to medical students from funds paid to medical schools for this purpose.

Nurse education activities, biometric studies, epidemiologic studies, and a public information and education program are being conducted by specialized staffs.

In 1957 the National Cancer Institute is working in a far different climate than the one in which it was established. No longer is cancer the "Great Darkness." Much light has been shed on it since 1937. There is a vast accumulation of new knowledge, new techniques, new instruments. Much that has been developed in other areas of medicine is available equally for the benefit of the cancer patient. There are promising leads in diagnosis and therapy, improved and increased numbers of facilities and services, better-trained professional groups to serve the cancer patient, and a much better-informed and cancer-conscious public—the essential first step in bringing the cancer patient to medical attention in time for him to have the full benefits of treatment. No longer is a diagnosis of cancer looked upon as a death sentence; the public and the press discuss cancer openly and freely, the same as any other disease.

The studies that have yielded negative results in the last twenty years are at least behind us. The same ground does not have to be gone over again and to that extent these studies are progress. Positive gains have been made along many lines of diagnosis and treatment and it would seem that as the knowledge thus gained is more widely applied it will be reflected in lower cancer mortality rates. A slight trend in this direction is indicated in the cancer death rate for females.

The advances that have been made in these twenty years are the work of many agencies and individuals in which the Institute is proud to have shared. There may never be a final answer to the cancer problem, but from where we stand in 1957 we can confidently expect discoveries in the near future that will greatly enhance our ability to control this disease.

Cooperation with the American Cancer Society

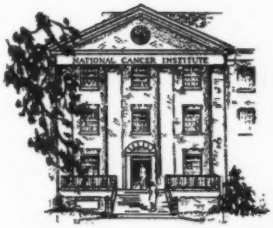
From the time of the Institute's establishment, cancer research and control activities in the United States have profited from the excellent liaison and cooperation that has existed between it and the American Cancer Society, the nation's largest voluntary cancer organization. Dr. C. C. Little, managing director of the Society in 1937, was a member of the first National Advisory Cancer Council. Other officials of the Society have served on the Council, the Institute's Cancer Control Committee, and other committees concerned with Institute activities. In turn, the Director of the Institute has for many years been a member of the Society's Board of Directors, and former Directors served in this same capacity. The Director and other Institute officials serve from time to time on various committees of the Society. Through close liaison, both organizations are kept informed of the program of the other so that time and money will not be wasted on duplication of effort. The two organizations have jointly

produced educational materials and sponsored research projects and the National Cancer Conferences held in 1949, 1952, and 1956.

Cooperation of Individuals

Continuously since August 5, 1937, and to a greater degree since the expanded program of the Institute began in 1947, representatives of the entire scientific community and leaders in all fields of work related to the cancer problem have given generously of their time and talents to assist in planning, developing, and evaluating the Institute's many and varied activities. These men and women have served as individual consultants, on *ad hoc* and long-term committees, study sections, and the National Advisory Cancer Council. Through their cooperation the Institute has been able to draw upon the wisdom and experience of the nation's leaders in cancer research, professional and lay education, cancer control activities, and public affairs in carrying out the duties assigned to it by Congress. They have contributed largely to whatever success has been achieved in the Government's cancer program and to them the Institute expresses its deep gratitude and appreciation on the occasion of its twentieth anniversary.

This report should not be closed without mention of the fact that at this twentieth anniversary there are on the Institute's staff a number of scientists and others who have given faithful service during the entire twenty-year period. Some of these were members of the cancer research group working in Boston, and others were working on cancer studies in the Pharmacology Laboratory of the National Institute of Health at 25th and E Streets, N. W., Washington, D. C., at the time the National Cancer Institute Act was signed by the President. These two groups formed the nucleus of the new Institute's staff. Members of this original staff who have been with the Institute continuously since that time, except for time spent in military service in World War II, are: Dr. Howard B. Andervont, Dr. Wilton R. Earle, Dr. Herbert Kahler, Dr. Mary Maver, Mr. Henry Meyer, Mr. John J. Murphy, Mr. Adrian Perrault, Mr. Edward L. Schilling, Dr. Murray J. Shear, and Dr. Harold L. Stewart.



Research at the National Cancer Institute

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THE Public Health Service had been actively engaged in cancer research when the National Cancer Institute was created. Dr. Joseph W. Schereschewsky had gathered a small group of unusually talented investigators in Boston to study cancer, while simultaneously Dr. Carl Voegtlin was directing the activities of a no less productive group in cancer research at the Hygienic Laboratory in Washington, D. C. The members of both groups were brought together on the Bethesda campus during the fall of 1939 and were joined by additional professional personnel whom Dr. Voegtlin had recruited during the two years intervening between passage of the National Cancer Institute Act and the opening of Building 6. This happy family of about forty investigators met at frequent intervals to discuss many facets of the research attack on cancer. The sessions were lively, sometimes with heated debates that continued long after the more formal meetings had adjourned. Everyone knew everybody—and probably had a fair insight into his attitudes or opinions, his work in progress, his goals, and his ambitions. There was no organization according to scientific disciplines; only the pathologists were grouped in an unofficial department. Almost all of the people who possessed doctoral degrees reported directly to the Chief of the Institute, who insisted on valid experimental design, strictly accurate observations, and reasonable, tempered interpretations of results. Reports for publication were circulated among one's colleagues, who commented for the benefit of the author. The environment was conducive to creative endeavor; the staff was busy and rapidly became highly productive. Teams of investigators developed on a basis of mutual interests and mutual respect. Leaders emerged, and those same individuals have retained their positions of eminence not only in the National Cancer Institute but also in the national and international aspects of cancer research.

The research program, as described in 1940,[1] reflected Dr. Voegtlin's sagacity and clearly represented the major interests of the staff. From the very beginning, scientists sought denominators common to different types of cancer but also focused attention on two specific anatomic

[1] VOEGTLIN, C., and SPENCER, R. R.: The Federal cancer control program. J. Nat. Cancer Inst. 1: 1, 1940.

varieties: carcinomas of the lung and stomach. The tools available for the job were experimental animals, efficiently equipped laboratories, and consumable supplies, controlled by an imaginative, industrious, highly talented, and sincerely interested staff. A need for clinical studies and for better knowledge of cancer as a disease of man was recognized. Plans for clinical investigation were made, but their realization at Bethesda required the passage of fourteen years.

The control of cancer requires practical means for preventing or effectively treating neoplastic diseases in all stages of development. Prevention can be realized only when causes are known. Therapeutically effective agents have been discovered by empirical approaches or by a well-reasoned analysis of facts obtained from scientific investigation. It becomes increasingly evident that one is unlikely to control cancer by studying cancers alone. Definition of their attributes in terms of physics and chemistry rests on advances in the natural and physical sciences, the discovery of new facts, new compounds of biological importance, and the ability to measure decreasing quantities of many things with increasing accuracy.

A chronicle of the accomplishments of the intramural research staff of the National Cancer Institute would require more space than this entire issue of the *Journal* provides. The objective of this report, therefore, will be limited to programs now existing, which will be described broadly, with some historical background.

Causation of Cancer

The total effort of many different individuals points to a large number of chemical, physical, and biological agents capable of eliciting cancerous responses in one or more species. The agents seldom possess other common attributes except those representing a chemically analogous relationship, but, even so, marked differences in potency are exhibited by compounds of closely related structure under given experimental conditions. Quantitative studies of dose-response relationships in carcinogenesis emphasize the need for referring precisely to the affected tissue and to the route of administration of the same agent for the same tissue; they also serve to reveal the different responses of individual tissues or organs to a common carcinogen and permit assignment of relative potencies to various carcinogenic chemicals. Pioneer studies at the National Cancer Institute of the carcinogenic hydrocarbons, azo dyes, and carbamates established correlations between chemical structure and carcinogenic potency. Members of the staff reported the first adenocarcinomas of the stomach and intestine and the first gliomas to be produced under controlled laboratory conditions.

Search for additional carcinogens has dwindled over the years as increasing emphasis is placed on their mode of action. Approaches of three general types continue to produce important information:

1) Modification of the carcinogenic response by manipulation of environmental, genetic, or physiological conditions.

2) Study by all available techniques of sequential changes occurring during transformation of normal cells to the malignant state.

3) Definition of the fate and distribution of series of analogous chemical compounds representing a spectrum of carcinogenic potencies in relation to the specific anatomical types of neoplasms produced.

The ability to elicit a considerable variety of cancers under controlled conditions has contributed importantly to concepts of cancer causation. There remains, however, the important problem of inducing, with facility and reproducibility, malignant neoplasms of the lung, stomach, colon, and rectum, with structural and biological attributes comparable to the tumors of those organs that occur in man. One suspects that the principles of chemical carcinogenesis, already established, apply equally well to these types of cancer, but either laboratory species are more resistant than man to production of such lesions, or classes of agents more importantly involved in their genesis remain to be discovered.

Information on the causation of human cancer has been obtained particularly with reference to occupations associated with markedly increased risk to one or more anatomic types of malignant neoplasms. Most of the environmental factors concerned apparently occur in the form of mixtures. Only a few pure compounds have been identified that unequivocally and individually elicit cancer in man. Continuing search is clearly indicated both to identify new hazards and to further characterize the noxious agent or agents among the mixtures now known or suspected to be potent carcinogens. Work of this type can be frustrating indeed. An association between the manufacture of chromates—from ore to finished product—and the heightened occurrence of pulmonary cancer among chromate workers has been established. Exposure of experimental animals to atmospheres contaminated with agents obtained from chromate plants or to mixtures of the important materials to which the workers may conceivably be exposed has failed to produce neoplasms of any organ. Subcutaneous injection of chromium, its salts, and materials intermediate between the ore and refined metal has also failed to elicit tumors. Nevertheless, the basic problem requires continuing study as a practical means of eliminating one known carcinogenic hazard from human experience. Equally pressing is the need for better definition of the relative roles of atmospheric pollutants generated by combustion of fuels, and the "excessive" smoking of cigarettes in the genesis of most pulmonary cancers. The laboratory evidence and, indeed, the epidemiologic findings now available for scrutiny are essentially similar.

One reasonable working hypothesis underlying all work on the many problems associated with environmental cancer would require that each neoplastic disease must have some cause which can be identified; another, that the term "spontaneous" is applied to the occurrence of cancer as a cloak for our ignorance in the same sense that "agnogenic," "idiopathic," or "essential" have been used in describing other diseases. Intensified,

diligent search for additional conditions seriously influencing risk to cancer in man is clearly indicated.

Not all such factors need be definable in chemical terms. Cancers due to excessive exposure to sunlight have been known for decades. The ultraviolet component of the solar spectrum has clearly been shown to be a potent carcinogen, and that segment responsible for tanning of the skin is most important. Recent research on photorecovery from certain injuries induced by ultraviolet irradiation in urodeles points to the need for similar work with more direct relation to cancer. Sunlight cancer of the skin is generally curable and also preventable. It seems rather surprising that the known facts have not been disseminated as widely through media of public education as have less well-established findings relating to the possible causation of other cancers. Much more attention has been given to pulmonary cancers, and, quite recently, the public press has become intensely interested in the carcinogenic potency of ionizing radiations.

Roentgen and *gamma* rays increase the frequency of some neoplasms in several inbred strains of mice and some of their first filial generation hybrids, even though the dose may be so small that the life expectancy is not appreciably reduced. The carcinogenic effects seem to be both direct and indirect. Hybrid mice exposed to total-body X irradiation develop more ovarian tumors than do mice that receive the same dose of X rays directly to the exteriorized ovaries. Shielding of the ovarian region during total-body X irradiation prevents occurrence of these tumors. Similar evidence is obtained from study of leukemogenesis. Grafts of thymic tissue from mice with high spontaneous risk of leukemia become leukemic when transplanted to suitable hybrid mice that have received total-body X irradiation. Treatment with ionizing rays is not essential to this type of leukemogenesis but accelerates the cancerous transformation.

The role of filterable viruses in the causation of cancers is receiving increasing attention. Detailed studies of the Rous sarcoma virus assume increasing importance through the application of precise quantitative biological methods. These facts emerge:

1) Rous sarcomas produced with small doses of the agent may contain no demonstrable virus.

2) Inbred chicks vary widely in their susceptibility to sarcoma production.

3) The dose of Rous virus used to initiate sarcomas has an important influence on the biological properties of the resulting lesion.

The apparent disappearance of virus from Rous sarcomas in a periodic, spontaneous, and unpredictable fashion has long been known. It would now seem to be explained by random fluctuations in sensitivity of the test objects and, perhaps, by the relatively small number of observations made in any given series rather than by the assumption of an inactive physical state on the part of the virus.

Preparation, from experimental tumors, of cell-free materials that strongly influence the occurrence of neoplasms in mice is an exciting new development. Subcutaneous injection of such preparations into mice less than one-day old is followed some months later by the development of leukemias and pleomorphic neoplasms of the parotid gland in susceptible hosts. Leukemogenesis is apparently accelerated, but the salivary-gland tumors seem to be new lesions. Incubation in tissue culture of the extracts from certain tumors enhances their infectivity, as shown by marked reduction in the latent period of tumorigenesis and the appearance of a wide variety of neoplasms in the treated subjects. Extracts or filtrates incapable of producing tumors may become highly potent after incubation *in vitro*. The nature of the carcinogenic agent or agents remains to be determined, and indeed the entire field of filterable materials relative to causation of human cancers requires exploration.

Interest continues in the mammary-tumor inciter that influences the occurrence of carcinomas of the breast when transmitted from mother to offspring through suckling. The National Cancer Institute actually ran a mouse dairy at one time in the course of numerous attempts to characterize the milk factor. Mammary neoplasms can occur in the absence of the Bittner agent. They seem to be scattered randomly through the pedigree, showing no tendency toward the familial distribution that characterizes the occurrence of breast cancers among stocks harboring the agent. Individual susceptibility plays a dominant role in production of mammary cancers insofar as the milk factor is concerned. It can be recovered from wild mice, in which a neoplastic response is seldom observed. Cross-breeding of mice of known genetic constitution has determined interrelationships of genic factors and the milk agent. The mammary-tumor inciter can be eliminated completely by altering genetic factors. That the agent actually disappears instead of lying dormant has been established, since no evidence of its activity can be demonstrated when cross-breeding techniques produce genetically suitable mice that would develop mammary tumors if the milk agent were present. These extensive experiments provide no evidence that the milk factor can originate *de novo* and have further demonstrated the effectiveness of the male in its transmission. The agent appears to be extrinsic rather than an endogenous product of cellular metabolism and possesses infectivity interrelationships similar to those demonstrated for microorganisms.

The study of factors involved in the origin of mammary cancer has required extensive research on sex hormones as carcinogenic agents. Availability of an ever-increasing number of compounds influencing the growth and development of gonads or secondary sexual organs has demonstrated the ability of some of them to influence the risk of cancers of various types. The exact relation of estrogens to the occurrence of mammary tumors remains to be defined. Anatomic and functional integrity of the breast requires some level of endocrine activity, and, perhaps, the data now available simply mean that continued estrogenization prolongs the life of mammary tissue beyond its normal span,

thereby permitting other important factors to bring about the cancerous change. This can scarcely be the case in leukemia, where no real evidence of dependence of the hematopoietic system on hormonal activity has been advanced. Estrogens in pharmacologic dosage clearly accelerate the development of mammary cancers in mice, but a carcinogenic hydrocarbon possessing no demonstrable estrogenic activity exhibits similar properties in suitable subjects. Progesterone also enhances the occurrence of mammary tumors in mice.

Long-continued suppression of thyroid activity by goitrogenic drugs administered to mice and rats is followed by the development of neoplasms in that organ. A decrease in the concentration of circulating thyroid hormone is thought to provoke increased output of thyrotrophic hormone by the anterior lobe of the hypophysis, producing hyperplasia, hypertrophy, and eventual thyroid neoplasms. Workers in other laboratories have observed that some thyroid tumors arise following protracted ingestion of diets low in iodine, which creates a situation biochemically similar to the effects of goitrogens.

Pituitary activity has also been implicated in the genesis of other neoplasms, notably those of gonads and secondary sex organs. Perhaps varied responses to estrogenic stimulation are determined in an important way by secretory activity of the pituitary gland, for not all strains of mice respond alike to a standard treatment with female sex hormone. Most recent evidence indicates a relationship between the dose of estrogen and the biological attributes of interstitial-cell tumors of the testes that follow its administration. Increasingly prolonged treatment accelerates the evolutionary process by which morphologically recognizable neoplasms acquire the ability to grow with almost complete disregard for the economy of the total organism.

The responses of heterogeneous populations of experimental animals to most carcinogenic stimuli have always been erratic with respect to frequency of tumor formation and to the time required for the neoplastic response to become manifest. Introduction of controlled inbreeding according to well-established genetic principles produced stocks of mice which were relatively homozygous long before the National Cancer Institute opened. These inbred strains are among the most important tools of cancer research. Their incidence of specific anatomic types of cancer remains constant within rather narrow limits, and even the age at which the neoplasms appear can be predicted. Their reactions to experimental procedures are uniform and reproducible. But these important subjects require the continuing attention of skilled geneticists if the stocks are to remain uniform. Mutations occur that provide additional important information on biological behavior, and unexplained changes in the occurrence of neoplasms have been noted on occasion. Certainly, variations in susceptibility to cancer induction among various inbred strains of mice are determined by genetic factors. A long-range program has associated seven specific genes, located on five different chromosomes, with the occurrence of spontaneous pulmonary tumors in mice. The same linkages influ-

ence the occurrence of neoplasms of the lung induced by some, but not all, of the chemical carcinogens tested. New cancers and non-neoplastic lesions result from cross-breeding experiments. One objective of the geneticist is to define those heritable traits that influence the individual's risk to cancer. Progress is slow, but attempts to associate physiological states rather than purely morphological variables with liability to tumor formation may provide means for examining comparable parameters in heterogeneous populations, including even man. An association, for example, between obesity as determined by the lethal yellow (A^y) gene and risk of pulmonary-tumor formation has been established for both spontaneous and induced lesions. Another strain of mouse becomes obese because of an entirely different genic influence, but no linkage between the *Ob* gene and susceptibility to pulmonary-tumor formation has been found. The problem is complex indeed.

One of the most important recent contributions has been the discovery of the site of action of the genes controlling production of pulmonary tumors, which was made possible through transplantation of lung tissues from two inbred strains, differing in genetic susceptibility, into a common host where systemic influences are equal. The inherent susceptibility or resistance to tumor formation, either induced or spontaneous, clearly resides within the transplanted tissue and cannot be influenced appreciably by the genetic composition of the host. Only a limited number of organs or tissues have been studied in this way, and extension of this highly significant finding is desirable. Experimentation elsewhere has revealed that the action of certain genes responsible for the production of mammary carcinomas in mice is manifested, in part at least, through the physiology of hormone production.

Much remains to be learned about the causation of cancer, and no other major area of research interest in the entire field of neoplastic diseases holds forth more hope for the benefit of mankind. Even should a common etiological denominator eventually be described for all malignant neoplasms, its effect will require participation of other factors extrinsic and intrinsic to the organism, which may well be multiple. A great deal has been learned about the origin and causes of certain experimental neoplasms. The staff of the National Cancer Institute published an exhaustive study on "Mammary Tumors in Mice" during 1945, which defined the complex interrelationships among hormonal, microbiological, and genetic influences, and to which little can be added at this time. Equally significant data will continue to accumulate with respect to other forms of experimental cancer.

The occurrence of clinical cancer is unequally distributed through the world and even within the United States. Groups of persons can be defined with extraordinarily high prevalence of specific anatomic types of malignant neoplasms, such as hepatic cancers among natives of subequatorial Africa. Study of the factors causally related to these curious phenomena seems practical and is highly desirable as a means of learning more about the origin of cancers affecting man. Carcinomas of the uterine

cervix are uncommon among Jewish women, more prevalent in non-Jewish white women, but even more frequent in colored women. Reasons for these discrepancies are being sought.

Mechanisms of Carcinogenesis

Definition of events that occur during the transformation of neoplastic cells to the cancerous state would contribute most importantly to our understanding of neoplasia. Ability to elucidate the sequential changes that are probably involved in cancerization presupposes a precise knowledge of normal cells, on the one hand, and the attributes of cancer cells, on the other. This has been achieved only in a practical sense. Pathologists do identify cancerous tissues with a high degree of accuracy but can predict the behavior of individual cancers in only the broadest general terms. Such concepts as initiation and progression, dependence and autonomy, sensitivity and resistance, which characterize some phase of the developing or fully developed cancer, require further study. These problems are still of major concern to biologists who create reproducible systems that ultimately permit chemical and physical approaches.

Mouse fibroblasts grown continuously in tissue cultures containing minute amounts of 3-methylcholanthrene have developed neoplastic properties and produce sarcomas when reintroduced into genetically suitable hosts. This work, first reported in 1943, was interesting in itself, but even more significant was the subsequent appearance of the same transformation among cultures of mouse fibroblasts to which no known carcinogen had been added intentionally. The transformation *in vitro* in the absence of known carcinogenic agents has been reproduced and has also occurred among some cultures of epithelial cells. This type of approach may eventually provide an excellent means of describing certain morphological and biochemical events associated with the development of cancer. There are, however, some extremely difficult problems that require elucidation before such studies become practical. The time at which the neoplastic transformation will occur cannot be predicted. The duration of the period during which the cells will produce sarcomas when injected into the proper hosts seems to be both self-limited and unpredictable. Perhaps the loss of transplantability reflects important changes in the antigenic structure of the cultures rather than a fundamental change in those attributes that may be functions of their malignancy. Total-body X irradiation of the host increases markedly the number of sarcomas that appear on injection of the cells into suitable mice. Equally important is the observation of high degrees of biological variance among individual clone cultures—cultures derived from a single cell—acquired in the course of time even though environmental conditions are standardized. These observations indicate the need for greater refinement of tissue-culture techniques.

Cells grown *in vitro* by techniques readily available in 1943 produced cultures of 20 to 50 mg. total wet weight. Chemical approaches to the study of cells growing under controlled laboratory conditions would be markedly

facilitated by availability of larger quantities of study material. Tissue culturists have now made possible the production of individual cultures containing 15 to 20 gm. of cells in some cases. Problems of growing different types of cells have been encountered and are being met. The difficulties of long-term tissue culture are quite different from those encountered in short-term propagation *in vitro*. Media to support cell growth have usually contained natural products, which vary in some unpredictable way from batch to batch and are seldom characteristic in their biochemical composition of the species whose cells they are expected to support. A chemically defined medium would provide far greater control. Some such media have been shown to support growth of a few cell strains but are incapable of permitting luxuriant growth of new explants from the generality of mammalian tissues. Addition of small concentrations of serum proteins enhances the biological effectiveness of chemically defined media. Cells introduced into any suitable tissue-culture medium modify their environment before they proliferate in a logarithmic fashion. Analysis of the chemical changes brought about in the fluid by the growing cells points the way for improvement of the supporting media. The already powerful tool of tissue culture is rapidly being sharpened for a variety of uses.

The concept of dedifferentiation or anaplasia as an attribute of cancer cells suggests that certain specialized functions possessed by their progenitors are lost during transition to the malignant state. Evidence of this is particularly strong from both morphological and biochemical studies. No system now available permits a reasonably direct sequential biochemical approach to this subject. One may study the normal or the cancerous. The number of cells destined to become cancerous even under the most severe stimulation is probably extremely small. Their identification is difficult at best and requires procedures that render the material unsuitable for biochemical study. It is practical, however, to study the acquisition of specialized form and function in developing embryonal cells.

Embryonic induction may involve the origin of relations and materials that form the basis for the relative stability of structure and function in the adult. Similar processes may operate when new subsystems arise in the adult and be reversed when adult stability of structure and function breaks down or is disrupted. To the extent that carcinogenesis represents the disruption of adult architecture, it may reverse or circumvent stabilizing mechanisms originating in inductive processes with particular reference to the influences of intercellular contacts and diffusible substances. Separation of renal and salivary-gland anlagen into their epithelial and mesenchymal components permits study of their interrelationships by ingenious tissue-culture techniques. The development of specialized structure by the epithelial cells depends to a major degree on the influences exerted by the connective tissue. Separated epithelium spreads at an interface as a thin, undifferentiated epithelial sheet or forms simple atypical projections; separated mesenchyme forms a homogeneous fibroblastic mass. Recombination of the two components immediately after

separation gives characteristic epithelial morphogenesis, but the morphogenetic stimulus declines in potency on continued culture of either component. Only the mesenchyme from the embryonal salivary gland is capable of evoking characteristic patterns in salivary epithelial cells; morphogenesis in the mesenchymal component of the metanephric anlage can be stimulated by its own epithelium and also by certain portions of the spinal cord. Inductions of this type are inhibited when cellophane separates the components but can occur when filters of larger average porosity, but which exclude passage of cells, are interposed between the two types of cells. Inductive activity appears to reside in large molecular materials produced by cells and confined ordinarily to their immediate vicinity.

One actively pursued chemical approach to the study of carcinogenic mechanisms involves investigation of the fate, distribution, and metabolism of *N*-2-fluorenylacetamide (2-acetylaminofluorene), identification and biological testing of its metabolic end products, and the testing of such analogues of the parent compound as may become available. *N*-2-Fluorenylacetamide produces a considerable variety of neoplasms in the rat, but the guinea pig resists its carcinogenic action. The use of isotopically labeled compounds greatly facilitates the studies. Most of the metabolic end products of *N*-2-fluorenylacetamide have been identified, the most prevalent in the rat being *N*-(7-hydroxy-2-fluorenyl)acetamide. The biological properties of these compounds are being determined. Recently acquired evidence suggests that at least two different enzyme systems, probably acting by separate pathways, may attack specific sites in the parent molecule. Differences in the excretion patterns produced by carcinogenic and noncarcinogenic analogues have appeared, and *N*-2-fluorenylacetamide is handled quite differently by rats and guinea pigs. Androgenic hormones accelerate the appearance of hepatic neoplasms in rats fed *N*-2-fluorenylacetamide; the level of riboflavine intake, on the other hand, has little influence on hepatic carcinogenesis with this compound in contrast to the important role played by riboflavine in the production of tumors of the liver with *p*-dimethylaminoazobenzene.

Evidence for binding of *N*-2-fluorenylacetamide by proteins of the liver during hepatic carcinogenesis is at hand. The amount bound in the liver exceeds the amount bound by other tissues. Two highly carcinogenic analogues of *N*-2-fluorenylacetamide are also bound strongly to hepatic proteins, while a relatively weak carcinogen of the same series is not. Functional derangement of the liver, as revealed by a radioactive Rose Bengal test used under strictly controlled conditions, is being correlated with structural alterations occurring during the administration of hepatic carcinogens and their noncarcinogenic relatives. This highly productive line of attack on mechanisms of carcinogenesis is a long-range program. It requires about 3 to 5 years to complete the isolation, identification, synthesis, and biological testing of a single compound. New types of neoplasms often appear in the course of the investigation as scientists learn how to focus the carcinogenic activity on a particular target organ.

Attributes of the Cancerous State

The National Cancer Institute was created at a time when the biochemistry of cancer dealt principally with the carbohydrate metabolism of neoplastic and normal tissues, which was stimulated by the pioneer observations of Warburg. Tumors, as a class, demonstrate high rates of aerobic and anaerobic glycolysis, and a diminished Pasteur effect is quite characteristic, so that active fermentation proceeds in the presence of oxygen. The basic facts are unassailable but their interpretation is by no means settled. While some workers have regarded the respiratory and glycolytic phenomena as the basic change in the transformation that is cancer, they are uniform rather than specific, and it now seems clear that tumors contain all the enzymes associated with glycolysis and with the tricarboxylic acid cycle. The low rates of glycolysis observed frequently among certain normal tissues may be associated with the ability of these tissues to accomplish the initial phosphorylation of glucose to hexose diphosphate.

An extensive comparison of activity of a number of individual enzyme systems and the concentration of several components in a wide variety of normal and neoplastic tissues in several species and strains of animals was conducted during the first years at Bethesda. The following general conclusions formulated in 1947 relate specifically to established transplanted tumors; additional data acquired during the intervening years reinforce the statements:

1) Each normal tissue possesses an individual pattern of enzymic activity by which it may be distinguished from all other tissues.

2) The same enzymes exist qualitatively in both normal and neoplastic tissues within the limits of the studies.

3) The enzymic pattern of a tumor is largely independent of its age, of its growth rate, or of the strain of animal in which it is grown.

4) The range of activity of each enzyme and of concentration of such components as the vitamins is much narrower among tumors than among normal tissues; *i.e.*, tumors possess a more uniform and less diverse chemical pattern than normal tissues.

5) When a normal tissue becomes neoplastic, many of its specific functional activities markedly decrease or are lost altogether.

6) The range of values for tumors is usually between the extremes of the corresponding values for normal tissues.

7) Tumors tend to converge, enzymically, to a common type of tissue. The nearly identical pattern of tumors suggests that they approach a chemically similar type of tissue.

Concepts of the biochemistry of cancer have also been aided by comparison of certain characteristics of normal adult liver, of fetal liver, of regenerating liver induced by partial hepatectomy, and of hepatomas.

The four homologous tissues fall into two metabolic and enzymic categories—normal adult and regenerating liver on the one hand, hepatoma and fetal liver on the other. Whenever the activity of any one catalytic enzyme in the hepatoma is less than, greater than, or equal to the activity of the same enzyme in normal adult or regenerating liver, the activity of the same enzyme in fetal liver is altered in the same direction. The findings have led to this clear summary of the situation: [2]

> "So far as has been calculated from the available data, it would appear that tumors function to the limit of their available catalytic systems whereas normal tissues have the advantage of a considerable reserve of such systems. The neoplastic transformation is evidently accompanied by a loss of this reserve. Like embryonic tissues, the tumor appears to possess a primitive economy. The luxury of reserve which the normal tissue enjoys must be the result of eons of evolutionary development."

Examination of peptidases that require a free *alpha*-amino group (aminopeptidases) reveals considerable rise in activity on conversion of liver to hepatoma. Further study has defined three separate enzymes of this general type that have different substrate specificities. Ability to separate the identities of the aminopeptidases discloses that one system rises, another disappears, and the activity of the third continues unchanged when liver becomes hepatoma.

The enzymes studied to date have all been lytic. Their connection with synthetic reactions characteristic of growing cells, both normal and malignant, is obscure. Further characterization of enzyme systems in tissues is a practical means of describing complex metabolic interrelationships and of acquiring information that will become critically important as the biochemist develops techniques for studying synthesis and relating his findings to physiological levels rather than defining capacities of enzymes in the arbitrary sense now required by most of the available techniques.

Indeed, the general aspects of protein chemistry and metabolism are critically important to cancer research, because these molecules are the most abundant constituents of cells, other than water, and are responsible for many structural and functional features of the mammal at all levels of organization. The strong preferences that many animals, including man, exhibit for levorotatory amino acids of the L configuration as precursors of proteins and intermediate compounds point up the need for providing, in practical quantity at reasonable cost, optically active enantiomorphs of amino acids with one or more asymmetric carbon atoms. The problem has been solved by the use of suitable enzymes to separate *N*-acylated racemic amino acids. The methods, already highly useful, are constantly being improved to effect greater economy and to meet particular demands.

Availability of amino acids in pure optically active forms of all isomers permits many types of studies. Absorption spectra of various amino acids and synthetic peptides prove fully as characteristic and specific as

[2] GREENSTEIN, J. P.: Biochemistry of Cancer, 2nd ed. New York, Academic Press, Inc., 1954.

melting points that permit unambiguous identification and quantitative estimation. Infrared absorption spectra of amino acids that possess only one asymmetric carbon atom are nearly identical in the 3 to 8 micron region, but diasymmetric amino acids differ so much in infrared absorption that identification of the spatial orientation of functional groups is possible. These accomplishments may serve as the bases for precise measurements of biologically important molecules in extremely dilute concentration.

The toxic properties of pure amino acids, given singly or in combination, have been studied. A hitherto unrecognized role of L-arginine in reducing acute toxicity of amino acids and the association of that toxicity with rising blood ammonium levels have been defined. The Krebs-Henseleit-Ratner cycle is clearly implicated. Administration of protective quantities of L-arginine with lethal doses of other individual amino acids has yielded a spectrum of responses with respect to blood levels of ammonium and urea. The biochemical evidence indicates a synergistic effect of glutamate and other compounds (many of them unrelated to each other) on the ability of arginine to lower blood ammonium.

A completely chemically defined water-soluble diet supports growth, pregnancy, and lactation of rats. The biochemist has apparently achieved complete control of the animal's dietary intake. It may become possible to define circumstances under which alternative pathways, available to the organism for achieving a given biochemical objective, are used by the intact subject under various conditions.

The development of new and better tools for biochemical investigation of growth processes has proceeded hand in hand with studies of intricate details of intermediary metabolism. The ability of glutamine to participate in transamination reactions with α-keto acids was first observed in 1950. More than thirty α-keto acids are capable of transamination with glutamine and asparagine to yield corresponding amino acids. The scope of known enzymic transamination has been extended to include compounds with a peptide bond. Participation of phosphorylated derivatives of pyridoxine, as coenzymes in some transaminase systems, has been further elucidated to show that reversible interconversion between pyridoxal phosphate and pyridoxamine phosphate is involved in the transamination mechanism. The role of pyridoxine derivatives in the glutamine transaminase system, however, remains to be established.

Much work has been done on peptide chemistry and the action of enzymes on synthetic peptides. It now becomes practical to synthesize peptides in which the optical activity of each constituent amino acid is known. Stereo-isomerism apparently influences some of the reactions of these interesting compounds.

The ability to isolate and characterize soluble proteins in undenatured form has been materially enhanced by the use of chromatographic techniques utilizing modified celluloses as adsorbents. A variety of methods has been developed to meet particular circumstances, and both cation and anion exchangers are available. Blood serum has been fractionated

to yield γ-globulins with different and specific immunologic properties, siderophilin, lipoproteins, proteins containing glucosamine, phosphatases, proteins that combine with vitamin B_{12}, hemoglobin and its protein complex, a trypsin inhibitor, albumins, orosomucoid, ceruloplasmin, thrombin, and a protein with electrophoretic mobility faster than albumin. Other proteins and other compounds have been separated, concentrated, and purified, such as the enzymes secreted by the pancreas, antibody proteins from γ-globulin, nonsteroid hormones, enzymes from various tissues, deoxyribonucleic acids, ribonucleic acids, and tobacco mosaic virus. Some of these accomplishments have required collaborative research with scientists in many different laboratories. The chemist can now separate a wide variety of proteins and related compounds and can characterize them in physicochemical terms, but other attributes of many of these substances remain to be determined. Serum albumin is separable into at least three electrophoretically distinct entities, which possess such closely similar antigenic properties that precise immunologic techniques cannot discriminate among them.

Growing significance is being attached to nucleic acid chemistry and metabolism in relation to neoplastic diseases. Realization of the heterogeneity of these complex molecules requires more precise methods for their isolation and identification. The approaches employed at Bethesda include physicochemical, enzymic, and cytochemical techniques. A single tissue contains a heterogeneous mixture of deoxyribonucleic acids, and these acids vary widely in their susceptibility to denaturation. New procedures have been developed for determining the extent of denaturation, and studies of diffusion and sedimentation constants of deoxyribonucleic acids permit calculation of their molecular weights that agree with results obtained from study of light-scattering effects. Highly polymerized ribonucleic acids prepared from rat liver and rat hepatomas have different molecular weights, and products formed by their hydrolysis yield different ultraviolet absorption spectra. Samples of ribonucleic acids isolated from rat liver and rat pancreas reveal no such differences.

Characterization of pyrimidine deoxyribosides from normal livers and hepatomas indicates important differences in these compounds intermediate between pyrimidines and nucleic acids. Deoxycytidine accounts for essentially the entire deoxyribosidic activity of the normal rat liver. Hepatoma differs in these respects:

1) The deoxyribosidic fraction accounts for only 50 percent of the total microbiological activity used in measuring these compounds.

2) Thymidine and deoxyuridine are present, as well as deoxycytidine.

3) Other unidentified compounds are responsible for a significant residual activity.

Studies of the regenerating rat liver also reveal changes in deoxyribosidic activity, so that the observations recorded above may reflect either

specific attributes of the cancerous state or qualities associated with rapidly growing cells.

A cell is complex indeed in terms of the structures it contains, the multitude of functions it performs, and the even greater number of biochemical reactions concerned with both structural and functional attributes. Dissection of cells by reasonably gentle physicochemical procedures permits topographical localization of some intracellular qualities that may be related to function. So rapid have been the advances in cytochemistry during the last twenty years that biochemists, in general, define the localization of newly discovered chemical reactions in relation to the several classes of intracellular particulates as a matter of course. The state of purity now achieved in isolation of mitochondria and nuclei is reasonably good, but the microsomal fraction usually obtained from disrupted cells must still be considered as a heterogeneous mixture. Further attempts are being made to isolate, in relatively pure state. intracellular bodies that can be defined by electron microscopy. Ferritin, visible within intact hepatic parenchymal cells and splenic macrophages, has been isolated and identified within the past year. A brisk controversy as to whether the Golgi apparatus represents a normal constituent of cells or a systematic artifact has recently been resolved by its cytochemical isolation from living mammalian cells. The Golgi substance seems to be concerned with the control of intracellular water balance and may occur in a greatly simplified form or be absent altogether from cells of highly undifferentiated cancers. The cytochemist has not yet contributed a means of discriminating between cancerous and normal cells, but his contributions to knowledge of function in relation to structure are of inestimable importance to the total effort in cancer research.

No consistent differences in the finer architecture of normal and cancerous cells have been described by the electron microscopist. Distinct differences in the appearance of two strains of cells with common ancestry, which represent relatively high and low degrees of malignancy, respectively, have been found recently. A broader search for differences among cells from cancers of common histogenesis that may reflect widely varying biological attributes is clearly indicated.

A given anatomic type of cancer, even one in which the individual cases seem to be composed of identical populations of cells, frequently elicits a broad spectrum of biological reactions and responses. The tumor smolders in one patient, advances rapidly in another. Such erratic behavior cannot be explained at this time, but the occurrence of experimental cancers, which require rather specific environments for their progressive growth, offers a means of approaching the problem. Neoplasms of the thyroid induced in rats and mice by prolonged administration of goitrogenic drugs usually grow only when transplanted to hypothyroid subjects. The tumors require stimulation by the thyrotrophic hormone of the anterior hypophysis. If these dependent tumors be propagated by serial transplantation, some of them will eventually acquire the ability to grow progressively in euthyroid subjects. Such neoplasms

have undergone some important change not always reflected in their histological appearance, which reduces their requirement for augmented stimulation by thyrotrophic hormones. The dependent tumors often concentrate and organically bind radioactive iodine, but the independent neoplasm usually loses much of its ability to perform certain biochemical functions characteristic of normal thyroid.

Estrogen produces testicular tumors composed of interstitial cells when administered in pharmacologic dosage to certain strains of mice. Frequently transplantation of these neoplasms is successful only in estrogenized hosts. Serial transplantation into suitable hosts will often permit development of cancers that will grow in the absence of estrogenic stimulation. The duration of estrogenization has an important effect on the biological characteristics of the interstitial-cell tumors, since the longer transplantation is delayed from their gross inception, the larger is the proportion of tumors that will grow independently of estrogenization. Moreover, more of the tumors transplanted soon after their initial appearance require estrogenization of the recipient for continued growth and evolution. No structural differences between the dependent and independent neoplasms are recognized.

Studies by others, notably Greene and Furth, have also shown that recognizably malignant neoplasms may acquire new biological characteristics. Tumors arising from organs or tissues known to require endocrine stimulation for their anatomic and functional integrity provide the best example of dependent and independent or autonomous types, but one example of a nonendocrine influence was reported in 1949. During May, 1940, hepatoma 31 originated at the National Cancer Institute in an Osborne-Mendel rat fed a diet containing *p*-dimethylaminoazobenzene. The neoplasm was propagated by serial transplantation in young rats of the same stock but grew rather erratically. Some regressing tumors could be stimulated to grow by supplementing the diet with comparatively large amounts of riboflavine or biotin, but a combination of the two was much more effective than either one alone. The striking stimulation of growth was not accompanied by increased consumption of calories or protein. The authors suggested[3] that:

> "The growth differential of malignant and nonmalignant tissues in the same host organism depends on a nicely balanced function of certain dietary factors which may produce either gain or loss of weight of these tissues, more or less independent of each other. This may possibly be accounted for by the drastic changes in biochemical organization resulting from the conversion of normal rat liver into hepatoma."

The ease with which most tumors can be propagated by serial transplantation has facilitated the study of many aspects of cancer, thanks to the active interest of geneticists who have produced inbred strains of experimental animals and defined the principles that permit transplantation of some tissues from animal to animal. The events occurring between

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[3] VOEGTLIN, C., and THOMPSON, J. W.: Differential growth of malignant and nonmalignant tissues in rats bearing hepatoma 31. Influence of dietary protein, riboflavin, and biotin. J. Nat. Cancer Inst. 10: 29–52, 1949.

the introduction of tumor cells and the vigorous growth of the established tumor have been studied by transparent-chamber techniques that permit direct microscopic observation. New technical developments permit one to transplant cells encased in membrane filters of known porosity, which allow exchange of fluids but exclude passage of cells. Thus the influence of humoral and cellular factors on the growth of cancers may be determined. Interposition of a finely porous membrane between the cancer cells and the host's own tissues permits the growth of a variety of ordinarily incompatible tumors, including those originating in foreign species, so long as cellular passage across the filter is prevented. Individual grafts of homologous tumors do not immunize their hosts unless the fragments develop a blood supply.

Among the unusual occurrences in the course of some clinical cancers are seemingly spontaneous remissions. Many have searched for antigenic differences between the generality of cancers and normal tissues, which would help to explain such bizarre events. It is not difficult to produce evidence for antigenic differences among tumors if one utilizes homologous systems. Mixture of ascites-tumor cells with cells immunized against the same neoplasm reveals close attachment of lymphocytes to individual tumor cells as a common prelude to death and disintegration of those cells. The same sequence can be observed when ascites-tumor cells are injected into immunized mice. The lymphocyte seems indeed to be a first line of defense, as suggested by Murphy years ago. Rapid death of ascites tumors in mice immunized more than two weeks prior to transplantation of the cancer, however, is not accompanied by a lymphocytic response. It takes some time for most antibodies to develop in response to an antigenic stimulus, and, probably, the delayed challenge occurs at a time when circulating antibodies have reached so high a concentration in body fluids that they are capable of destroying the invaders without participation of lymphocytes. These findings imply an important role of the lymphocyte in antibody production, in keeping with information obtained by others.

The precise nature of the antigenic stimulus leading to immunity in homologous subjects is not established, and, indeed, it may be more closely related to the individuality of the donor than to the cancerous nature of the transplanted tissue. A means, too drastic for practical application, of breaking down natural resistance to the growth of transplanted tumors or of normal tissues has been described. The effects of total-body X irradiation on mice have been an important segment of the Institute's program for a long time. A lethal dose of X rays destroys the bone marrow and lowers the body's defenses against bacterial invasion so that overwhelming sepsis commonly ensues. Dramatic protection against lethal toxicity is afforded by intraperitoneal or, better, intravenous injection of isologous or homologous bone marrow within a few hours of exposure. The same morphological evidence of bone-marrow damage is seen, but the organ recovers. Substantial evidence indicates that the cells which repopulate the marrow spaces are derived in con-

siderable part from the injected donor cells. Mice that have been protected from acutely lethal doses of total-body X irradiation can accept genetically inappropriate tumors and skin. The skin grafts remain healthy for an indefinite period.

Resistance to growth of transplanted tumors can be broken down in some cases by permitting one neoplasm to attain a large size, after which the host often will accept a genetically incompatible tumor graft. The success of late inoculation is interpreted as a reflection of the general deterioration in the condition of the host resulting from the presence of a large tumor and not as a specific immunologic effect.

While much has been learned from study of immunity against homologous transplanted tumors, the system used is a far cry from the situation in which one individual demonstrates some type of resistance against his own individual cancer. Individual mice of an inbred strain are almost as alike as identical twins. Recent claims for demonstration of antibody production by experimental cancers produced and studied within an inbred strain of laboratory mice represent an exciting new development in the field of cancer immunology. A rigidly controlled experiment at Bethesda has disclosed the ability of fibrosarcomas induced by 3-methycholanthrene to induce a resistant state to transplantation within the original host strain. Spontaneous fibrosarcomas or normal tissues do not elicit a comparable response.

Further experience with protection against acute lethality from total-body X irradiation by transplantation of healthy marrow has elicited important information. Leukemias arise some months after treatment, and some of them can be shown to originate among the donor cells that repopulated the bone marrow. Isologous bone marrow affords somewhat greater protection than does homologous marrow with respect to survival during the first thirty days after exposure. Thereafter, isologous marrow is clearly superior, since recovery of the subjects receiving homologous marrow is limited by the onset of a secondary syndrome marked by weight loss in spite of a normal food intake, degeneration of lymphoid tissues, occasional dermatitis, and occasional hepatic lesions. Many of these animals die after a long illness, but some survive. The secondary phase has become the focal point of much work upon its causation, prevention, and treatment.

Deterioration of the cancerous host may be lethal in itself, increases morbidity, and may prejudice the patient's response to therapeutic procedures. Continuing growth of cancer requires building blocks for all the complex compounds contained in its protoplasm. While no discrete qualitative differences have been described among the classes of proteins, nucleic acids, or other constituents of cancerous protoplasm that clearly distinguish it from normal protoplasm, the sequestration of materials within the cancer seems to have important consequences for the economy of the cancerous host. The diet usually provides adequate quality and quantity of essential metabolites, but loss of appetite may so restrict the supply of these important nutrients that the progressive growth of the

malignant neoplasm is accomplished by withdrawing those substances needed for the growing tumor from the host's relatively normal tissues. The host loses weight. The mechanisms concerned in the translocation of nitrogenous building blocks are completely obscure. Incorporation of lyophilized tumor into the diet permits the growth of cancer to proceed without significant weight loss from the carcass. This is not solely a matter of appetite but, rather, an increased efficiency of synthesis of tumor tissue. The problem is being approached in several ways, including the indirect measurement of energy metabolism by a self-recording analytical respirometer.

Depression of catalase activity in the presence of normal levels of many other enzymes in the livers of cancerous hosts was established as a regular consequence of progressive growth of malignant neoplasms in the early days of the Cancer Institute. Continuing study of this phenomenon has been highly profitable. It has required the development of precise methods for measuring catalase activity and the isolation and identification of specific hepatic proteins that possess catalase activity. The striking reduction of hepatic catalase resides in the readily extractable protein fraction of livers from tumor-bearing rats. No evidence for a catalase-inhibitor complex or a structurally altered catalase has been observed but, rather, a large, highly active, labile component of hepatic catalase disappears completely during the growth of cancer. The mechanism by which hepatic catalase activity is depressed remains obscure, but evidence that a humoral factor may operate has been advanced from several sources. These facts are well established:

1) A soluble nondialyzable fraction of homogenized tumor tissue lowers hepatic catalase when injected intraperitoneally into noncancerous rats.

2) Injection of cell-free fluid from ascites tumors has a similar effect.

3) Feeding cancerous tissue for 3 days will lower hepatic catalase activity to a greater degree than will feeding of normal tissues.

This research has been extended to include other iron-containing proteins with most important consequences.

A spectrum of anemias representing a variety of causes develops during the course of some cancers. Destruction of erythrocytes at a rate more rapid than their production characterizes a substantial number of anemias found in patients with advanced clinical cancers. Reproduction of the basic features of this clinically important syndrome in rats bearing experimental cancers has been accomplished. The anemia is due to a rapid loss of erythrocytes from the blood into the tumor as a result of hemorrhage or thrombosis. The experimental neoplasms that produce anemia may contain as much or more iron than the liver of the host. No evidence for intravascular hemolysis can be demonstrated. The fundamental factor seems to be sequestration of a major part of the body's iron within

a useless and metabolically inaccessible compartment. There is no evidence that the same process has anything to do with reduction of hepatic catalase activity.

Hypoalbuminemia also occurs commonly in patients with advanced cancer. Independent measurement of total plasma volume and circulating red-blood-cell mass reveals no major increase in plasma volume and has permitted recalculation of conflicting data published in the medical literature to reconcile the divergent views expressed. The possibility of increased utilization of serum albumin has been explored. A significant decrease in total exchangeable albumin has been found in advanced cancer, but the turnover rates for albumin are commonly lower than those observed in healthy subjects. Hypoalbuminemia in cancerous individuals would appear to be due to a primary decrease in albumin synthesis.

Fever, a common phenomenon among leukemic patients, has sometimes been ascribed to the disease itself. An intensive systematic study of this subject has been a joint effort of the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, and the Division of Biologics Standards. The great majority of febrile episodes have been due to complicating and remediable bacterial infections, as shown by the ability to isolate and identify microorganisms during the febrile state and prompt defervescence following institution of appropriate therapeutic procedures. The marked susceptibility to bacterial infection is often demonstrated by recovery of relatively avirulent organisms from specific lesions; yet, such bacteria as coagulase-positive *Micrococcus pyogenes aureus* and *Pseudomonas aeruginosa* cause serious clinical infection. The latter organism, in particular, produces general sepsis that is extremely difficult to treat. Some febrile episodes persist despite failure to detect objective evidence of infection, but among these patients are some who ultimately develop overt bacterial infections. No difference has been observed in the opsonocytophagic indices of mature polymorphonuclear leukocytes in healthy and leukemic subjects. Heightened susceptibility to infection apparently relates to the ratio of mature polymorphonuclear leukocytes to the total number of circulating white blood cells rather than to the absolute number of circulating polymorphonuclear forms. No impairment of antibody response has been detected among leukemic patients challenged with a variety of bacterial or viral vaccines.

Spontaneous bleeding accompanied by thrombocytopenia also complicates the course of some leukemias and may be a terminal event, especially in acute leukemias of childhood. Correction of the platelet deficiency *in vitro* corrects completely the clotting of blood in the test tubes. A double-blind comparative study of the relative efficiency of fresh *versus* banked blood in arresting the tendency to spontaneous bleeding clearly establishes the great superiority of the former. Fresh blood has produced clinical benefit in some 70 percent of the patients studied, whereas no significant response has followed transfusions with blood from the bank.

Familiarity with the attributes of the cancerous state is not sufficiently

extensive to provide a basis for designing an all-inclusive therapeutic agent for cancers and, indeed, the knowledge now available discourages the hope for such a panacea. The evidence also suggests that changes in body fluids measurable by chemical means occur only after many cancers have achieved some critical size, which varies widely from case to case.

Therapeutic Research

Ability to find more cases of cancer while the cells are confined to their original site would greatly enhance the value of those surgical and radiological procedures which remain the most effective means of curing cancer today. Patients hospitalized by the National Cancer Institute at the Clinical Center are referred by competent medical authority, almost always the attending physician, to participate in programs of clinical investigation reflecting the current interests of the staff. This does not permit the study of cancers as they occur in a general population. Other long-established organizations are well equipped and well staffed for such studies and can explore better the possibilities and problems associated with devising better case-finding and diagnostic techniques.

The surgical program is concerned with the benefits to be derived by the patient from the use of radical surgical procedures for treatment of cancers of the head and neck and of the female pelvic organs. End results are not yet available. Many operations utilizing the basic principle of dissection *en bloc* fail because of local recurrence of the cancer at the operative site even though the surgical techniques be meticulous. It is possible in some cases to identify individual cancer cells, even bits of cancer tissue, in washings made from the wound immediately before closure. Limited experience to date suggests that subsequent local recurrence is equally frequent in contaminated and uncontaminated fields. A problem has been defined, rather than settled, and the ultimate answer will require broader experience than can be obtained at the National Cancer Institute. Laboratory studies to devise means of sterilizing wounds in experimental animals deliberately contaminated with cancer cells are in progress.

Both 250 kv. and 2 Mev (million electron volts) X-ray machines are available for radiological therapy and research. A unique 3 Mev Van de Graaff electrostatic generator was generously given to the Institute by the Liggett and Myers Tobacco Company, which has now been modified to produce a clinically useful fan-shaped beam of electrons with initial energy of 2.1 Mev. Maximum penetration is 1.0 cm. Weekly doses of 300 to 450 rep (roentgens equivalent physical) may be given to the skin of the entire body at a single time, with eventual total doses of 1000–3000 rep without producing systemic effects in patients with mycosis fungoides. These patients show improvement from electron beam therapy, though in no case has the disease been eradicated completely. The design of gels containing chemical substances that change their composition when bombarded with electrons has provided a practical and precise dosimetry.

Another limited study on prolongation of treatment time as a modifier

of clinical response in X-ray therapy of epidermoid carcinoma has extended the treatment over 100 days with an increase in total dosage to as much as 10,000 r. The treatment is not always cancerocidal, and normal tissues have been severely affected in some cases. Most striking benefit is observed when the neoplasm, and therefore the total amount of tissue to be irradiated, has a limited extent. Undesirable effects are due as much to the volume of tissue exposed to the beam as to the large dose employed.

Experimental tumors provide a spectrum of radiosensitivities. Various alterations of the treatment schedules have been studied in an attempt to improve the therapeutic efficacy of ionizing radiations. Small doses of X rays to the entire body increase the radiosensitivity of the locally irradiated lesions for at least two different types of experimental cancers. Attempts to reproduce the acquisition of resistance to ionizing rays seen frequently among recurrent tumors in clinical practice have been unsuccessful in laboratory studies.

Comparatively little is known about the effects of ionizing rays on protoplasm in other than a gross sense. Investigation of their effects on such simple systems as aqueous solutions of glycine or alanine has led to description of four reactions. One reaction results directly from absorption of energy by the dissolved molecule, the other three reactions being indirect effects of hydrogen ions, hydroxyl ions, and hydrogen peroxide produced by energy absorbed by water. Secondary and subsequent effects relate to the action of the free radicals with molecules in the irradiated medium.

Study of acquired photosensitivity by actively growing respiration-deficient haploid yeast cells provides a model system that may be useful in learning more about the effects produced by X rays on cells. These particular yeast cells are lacking in certain cytochromes. A hemochromagen with spectral characteristics of a hemoprotein increases as the cells develop sensitivity to light. The curve for acquired sensitivity is consistent with the hypothesis that the photolethal effect is associated with an increasing concentration of the pigment.

The effect of X irradiation on mammary-tumor implants growing in transparent chambers in the skin of mice, reported in 1950, described an important role played by blood vessels. One day after exposure to 2000 or 3000 r, a slight opacity was noted in the tumor, caused by direct action of irradiation on the tumor cells. The opacity increased. The blood vessels supplying the neoplasm narrowed progressively "... clearly because the tumor tissue stopped growing; and when growth was resumed, the vessels enlarged again. The growth rate of regrowth foci was the same as that of nonirradiated tumor tissue, but since no new capillaries were produced the vascular supply became inadequate and growth was slowed. The vessels within the regrowth foci broke down and the nonvascularized, relatively opaque tissue aroused a series of reactions resulting in the ingrowth of nonirradiated vessels into the irradiated zone. . . . That irradiated vessels could not produce new ones was demonstrated, not

only by the vascular abnormalities of regrowth foci but also by the inability of an irradiated bed to vascularize tumor implants or host-formed cellular layers." [4] Subsequent studies have elaborated the effects of X rays on the capacity of endothelium to produce new vessels in greater detail.

Many cancer patients first seek medical advice when their tumors have already metastasized and are beyond the hope of definitive treatment by surgical or radiological means. This may not become apparent immediately, for ability to recognize minute deposits of cancer cells is seriously limited. The course of cancer in some patients has suggested that excision of a primary cancer has had an important influence on the growth of undetected distant metastases, which then seem to flourish. This situation has been studied lately in experimental systems, and at least one transplantable tumor exists in which amputation of a tumor-bearing extremity is followed by vigorous growth of pulmonary metastases that would otherwise have remained invisible to the naked eye. The experimental design precludes any possibility that surgical intervention influenced the dissemination of the tumor cells. Much more experience of this type is needed.

The principal therapeutic problem in cancer today is the effective management of disseminated cancer. Great impetus has been given to search for a cancer remedy that might be effective on systemic administration by the studies of Huggins on the arrest of growing prostatic cancer by administration of estrogen and/or castration. The use of sex hormones in the management of advanced cancers of the breast and prostate is now accepted in most clinics throughout the country as effective though limited palliation for some, but not all, patients. Massive parenteral estrogen therapy with water-soluble compounds, first devised for the treatment of mammary cancer by a member of the Institute's staff, is now widely accepted and has facilitated development of dosage regimens for treatment of various gynecologic disorders. Consequently, three preparations of parenteral estrogen are now available from commercial sources. No clear superiority over more conventional treatment has been demonstrated for massive parenteral estrogen administration in patients with mammary cancer, but it is a practical and effective procedure. Experience with intravenous androgen therapy, on the other hand, has been disappointing. Difficulties have been encountered in developing satisfactory preparations for intravenous use, and even the best preparations are tolerated rather poorly. Hormonal activity as measured by bioassay rapidly disappears from the blood stream.

A clue to one possible way in which sex hormones may interfere with cancerous growth is afforded by biochemical investigation. Glycolytic metabolism of cancer cells is markedly reduced *in vitro* by addition of minute amounts of estrogenic substance to the medium. Exposure of tumor-bearing mice to elevated environmental temperatures retards the

[4] MERWIN, R., ALGIRE, G. H., and KAPLAN, H. S.: Transparent-chamber observations of the response of a transplantable mouse mammary tumor to local roentgen irradiation. J. Nat. Cancer Inst. 11: 593–623, 1950.

growth of the cancers, at which time slices of the neoplasms reveal decreased glycolytic activity. Insulin overcomes the action of sex hormones on glycolysis, as studied *in vitro*, but has less effect on decreased fermentation resulting from temperature stress. The same systems studied with homogenates instead of slices has revealed that addition of hexose diphosphate to the preparation prevents decay in the glycolytic rate, while a tiny amount of crystalline zinc insulin increases the rate of glycolysis. The primary reaction observed may concern insulin and anti-insulin compounds that interfere with the conversion of glucose to hexose-6-phosphate, an early step in the process of carbohydrate metabolism. Exploration of additional tumors indicates considerable variability in their responses to the postulated insulin : anti-insulin system. The ability of a given compound, with or without hormonal activity, roughly parallels the capacity of that agent to induce necrosis in an experimental neoplasm.

About ten years ago a relationship between folic acid and estrogenic action was described, since the genital tract of the folic-acid-deficient chick exhibited a very limited response to excessively high doses of estrogen. Similar impairment to estrogen response in the folic-acid-deficient monkey was soon established. Subsequent availability of antifolic and antipurine compounds permitted quantitative study of their interference with estrogen-induced growth. These basic observations have been extended to the treatment of choriocarcinoma. An unconventional regimen for the administration of methotrexate or 6-mercaptopurine has been employed in suitable patients with high urinary and plasma levels of chorionic gonadotrophin resulting from these cancers. Data obtained from such highly individualized studies support the conclusion that short, intensive courses of antimetabolite therapy are well tolerated, provided adequate opportunity is permitted for recovery from undesirable effects of the drugs and that urinary gonadotrophin titer may be actually depressed by any single course of treatment and will return in a few days to its prior level or to substantially lower levels. Some patients receiving well-controlled, repeated treatments have ultimately reduced their secretion of chorionic gonadotrophin to normal levels and have remained in apparently good health. These vagaries in clinical behavior of chorionic tumors demand utmost conservatism in evaluation of the therapeutic effect, but the limited experience already obtained requires intensified study of additional patients because of the reproducible suppression of metastatic tumor growth that has been observed.

Search for other compounds to counteract sex hormonal activity has revealed that amphenone (1,2-bis(*p*-aminophenyl)-2-methyl-propanone-1) shows moderate anti-estrogenic activity in the chick oviduct test and has progestational activity. The adrenals of rats to which amphenone had been administered were more than twice normal size, appeared yellow rather than reddish-brown and, on histological examination, the cortical cells of the fasciculata and reticularis were laden with fat; the thyroids were also enlarged. The adrenal changes suggested some interference

with corticoid synthesis, which has been amply confirmed by all subsequent research on amphenone. Remissions in cancerous growth reported following adrenalectomy, and the possibility that amphenone might interfere with the growth of adrenal carcinomas, made clinical trial of the new drug imperative. Sedative effects have been noted as undesirable side reactions of amphenone therapy; yet, unequivocal evidence of inhibition of adrenocortical activity has been obtained. The drug is an extremely useful experimental tool. It has failed to arrest the growth of carcinomas arising from adrenocortical cells but does suppress the synthesis of hydrocortisone and corticosterone in man. Hypertension, diabetes, and mental aberration consequent on hyperadrenocorticism due to cancerous growth have been reversed repeatedly. So precise are the clinical investigations of patients treated with amphenone that intimate biochemical relationships of compounds produced or influenced by adrenocortical activity are being defined through collaborative efforts with investigators in several different clinics. Amphenone should be regarded as a prototype drug. Development of analogues which may retain its important endocrinological influences without its undesirable side reaction, though unsuccessful to date, is a continuing important effort at the National Cancer Institute.

Cancer research has benefited materially from endocrinological approaches, and particularly from precise study of abnormalities of somatic development resulting from endocrine dysfunction. The influence of the central nervous system in endocrinological responses is becoming increasingly important. Destruction of specific areas in the anterior hypothalamus of the rat causes change in the behavior of all endocrine glands. The hypertrophy of the thyroid gland following treatment with thiouracil is prevented. Persistent estrus or prolonged diestrus can be produced, in which case the normal estrous cycle is restored by daily treatment with progesterone. Adrenal and testicular atrophy follow destruction of small areas about the tuber cinereum. Thyroid function is retained in hypophysectomized mice that receive intraocular transplants of pituitary tissue, even though all endocrine target organs atrophy. The activity of the thyroid gland in such subjects can be changed by altering the level of circulating thyroxine, but this does not influence the size of the thyroid.

Endocrinological research requires batteries of quantitative bioassay procedures and precise chemical methods to be really effective. Availability of such resources is essential to the comparison of the endocrinological effects of similar molecules, such as the discovery that 19-norprogesterone is much more active physiologically than progesterone itself, the first step in focusing attention on nor-steroid activity.

Possibility that systemic administration of an agent might seriously damage cancers was recognized by a member of Dr. Schereschewsky's group in Boston when Shwartzman and Michailovsky [5] reported that parenteral administration of a bacterial filtrate produced hemorrhage and

[5] SHWARTZMAN, G., and MICHAILOVSKY, N.: Phenomenon of local skin reactivity to bacterial filtrates in the treatment of mouse sarcoma 180. Proc. Soc. Exper. Biol. & Med. 29: 737-741, 1932.

necrosis in mouse sarcoma 180, that some of the tumors regressed completely, and that the normal tissues of the mouse were unaffected. The results were confirmed and by 1936 a small-scale, systematic search for drugs that would damage cancer had been instituted. Bacterial filtrates were studied intensively in the early days at Bethesda, and increasingly purified and potent preparations were made. Activity was finally identified with complex polysaccharides produced by many gram-negative bacteria. Some experimentally induced neoplasms as well as transplanted tumors could be seriously damaged by polysaccharides from *Serratia marcescens*. A limited clinical trial was conducted in 1939 on patients with advanced carcinoma of the prostate with widespread osseous metastases, multiple myeloma, lymphosarcoma, and Ewing's sarcoma, respectively. Some of the lymphosarcomatous masses disappeared. The two patients who showed noteworthy relief of symptoms also presented chemical evidence of rapid breakdown of nitrogenous substances. Each patient died with tumor, but the lapse of weeks between first treatment and necropsy made it impossible to determine whether the first treatment produced hemorrhages similar to those seen in animal tumors a short time after injection. Polysaccharide preparations developed to date induce a state of resistance in subjects after the first injection. Further developmental research in another laboratory was reported to have reduced the toxicity. Some few patients appear to have been markedly benefited by their administration, in a joint study initiated by the National Cancer Institute in 1943 in Philadelphia. The over-all experience suggests that the polysaccharides are similar in their reactions and limitations to Coley's toxins, which, of course, were prepared from cultures of bacteria. The final chapter remains to be written on polysaccharides as anticancer agents, since a variety of similar components possessing similar properties was recently shown at the National Cancer Institute to be extractable from mammalian tumors and normal tissues.

The increasing importance of polysaccharides has encouraged the staff to determine the general importance of those complex molecules in the biological cosmos. Gram-negative bacteria have been considered the only natural source of polysaccharides which induce, in mammalian systems, a syndrome of reactions including fever, changes in concentration of circulating leukocytes, Shwartzman phenomena, tumor damage, and a series of profound vasomotor disturbances terminating in a shocklike state. A large number of polysaccharide complexes isolated at the National Cancer Institute from normal and neoplastic mammalian tissues and from plants share some of the properties exhibited by bacterial products. A group of polysaccharides has been selected for further study from the larger population. Some of them produce damage in experimental tumors and elicit the entire spectrum of host responses heretofore considered unique attributes of bacterial endotoxins. Those polysaccharides found to be ineffective in damaging tumors consistently exhibit little or no other activity. The profound effects of the active polysaccharides on a basic defense mechanism, the properdin system, important in itself, may

possibly illuminate the mechanism by which these agents produce necrosis of tumors and the nature of the resistant state induced by polysaccharide treatment.

The question naturally arose as to whether the necrosis produced in some cancers was a property unique to polysaccharides. A broad program was instituted during the early forties that screened a wide variety of chemical compounds and agents from natural sources for ability to produce necrosis in sarcoma 37 on a single injection into the host. This was a litmus paper test to focus attention on materials that damaged experimental neoplasms. Of some 3,000 compounds examined, several hundred agents were found to necrotize sarcoma 37. The majority produced the effect with a dose that approximated the maximum tolerated by the host. Such great toxicity has discouraged the introduction of most of these materials into clinical investigation, but some of them warrant further study.

Among the more interesting of the agents screened were preparations made from roots of the May apple, *Podophyllum peltatum*, which produce cytological alterations in normal epidermis and in condylomata. A single, subcutaneous, sublethal dose of podophyllin, podophyllotoxin, or α-peltatin produced hemorrhage and necrosis in sarcoma 37 and retarded the growth of other experimental tumors. Podophyllin caused mitotic arrest, distorted chromosomal distribution, and multinucleation, as well as necrosis, in sarcoma 37 and also in intestinal epithelium. α-Peltatin, β-peltatin, and podophyllotoxin were studied thoroughly for their effects on five different transplantable mouse tumors. A single injection of each of the compounds induced extensive damage in all of the tumor types investigated. Metastases responded like the main tumor mass. Multiple injections retarded the growth of the tumors in treated as compared with untreated mice, and particular dosage schedules resulted in a slight increase in survival. The response to α-peltatin of patients with various disseminated cancers was investigated at the Public Health Service Hospital in Baltimore, where the National Cancer Institute had maintained a small clinical research unit. The study yielded interesting pharmacologic effects rather than therapeutically valuable ones. Research on the chemistry of podophyllin derivatives required participation of organic chemists who have described the absolute configuration of lignans, thereby establishing the steric requirements for tumor-damaging activity among this group of compounds.

The screening program has been greatly reduced since 1952. By that time a sufficiently large number of tumor-necrotizing agents had been acquired as tools for systematic investigations and attention was directed to study of the mechanisms by which these drugs produced their effects. Podophyllotoxin and its derivatives have been used as prototypes, and a water-soluble member of the group, acetylpodophyllotoxin-ω-pyridinium chloride, has been especially useful. Decreased enzymic activity in the damaged tumors is not related to any particular association with subcellular structures. Disruption of tumor cells by physical means, such as

ultrasonic vibrations, produces different changes in enzymic activity from that characteristic of drug action. Attention has focused on the impairment of glucose metabolism as a major consequence, associated with pronounced decrease in diphosphopyridine nucleotide (DPN). The normal rate of glucose utilization can be restored in the damaged cancer cells by addition of this coenzyme in large excess. The efforts of two groups of investigators starting with *in vitro* and *in vivo* approaches and with completely different initial objectives are now converging to describe the effects of cancerous growth on the capacity for the liver of the cancerous host for DPN synthesis, as well as the importance of this compound in the action of several anticancer drugs.

Anticipating the opening of clinical facilities at Bethesda, a group of investigators was established at the Laboratory of Experimental Oncology, at the University of California, during 1947. Clinical investigation received major program emphasis during the seven years of its existence. Some 492 patients were studied, all of whom had hopelessly incurable disease. The gross five-year survival rate was 7 percent despite a large proportion of patients with acute leukemia in the group. Therapeutic research stressed the use of new drugs then appearing from several sources, which were sometimes given by intra-arterial routes. Study of the influence of transfusions and antibiotics upon the duration of life in children with lymphocytic leukemia showed a significantly prolonged survival time among patients so treated, as compared with untreated leukemic children, with those receiving irradiation therapy in addition to blood transfusions and antibiotics, and with children whose leukemias were treated with blood transfusions alone. Another investigation of a small group of children with acute leukemias indicated that effects of corticotrophin and of cortisone were palliative. Duration of life was not increased by the use of those hormones. The staff emphasized the necessity for statistical comparison of patients treated experimentally by chemotherapeutic agents with an adequately controlled comparable group. The occurrence of almost complete remission in the course of acute leukemia following acute infections was recorded. The first surgical hypophysectomy for cancer was performed at the University of California and studied jointly with the staff of the Laboratory of Experimental Oncology. The operative procedure was complete, for the patient developed typical signs of panhypopituitarism, but no definite effect on the progressive growth of his disseminated melanoma was observed. Studies on the blood supply of tumors in man established increased blood supply and rate of flow, abnormal arterial patterns, increased capillary permeability to fluorescein, and increased oxygen content of venous blood draining malignant neoplasms as characteristic. The important role of the lung in removing leukocytes from the circulation was clearly demonstrated. A series of reports on the natural history of several anatomic types of cancer has analyzed factors influencing survival and provided a type of information that is badly needed on a larger scale as reference standards for therapeutic research.

Inauguration of clinical research at Bethesda in 1953 provided a small complement of beds and clinical staff, which has been gradually increased until the full allotment of 139 beds was activated during June 1957 to permit the full-scale utilization of modern medicine in the study and care of the cancer patient. Prolonged discussions of experience, both here and elsewhere, with a liberal admixture of conjecture have guided the evolution of an intramural chemotherapy program to identify and investigate those agents that damage cancers and exhibit no endocrine or other biological activity which impels deviation from the general guidelines. The objective of the program is clinical—effective treatment of cancer in man—necessarily supported with whatever laboratory activities may be required. It is considered that the scope of the program should include:

1) Selection and procurement of agents.

2) Their evaluation in various types of laboratory screens, including the responses of cancers in experimental animals.

3) Study of pharmacology and toxicology in large laboratory animals of those agents surviving the laboratory screening procedure to provide information needed before the drugs are administered to patients.

4) Testing the effectiveness of selected agents on patients with accessible cancers by injecting minute quantities directly into superficial lesions, essentially an additional screening device at a human level.

5) Systemic administration of selected agents to selected cancer patients for therapeutic trial, including clinical pharmacological study necessary to determine blood levels, distribution, excretion, and metabolic alterations of the agents.

6) "Feedback" to the laboratory of the preliminary data acquired from clinical study for whatever studies may be indicated, such as further delineation of mechanism of action, correlation of effectiveness in tumors of patients and of animals, correlation between chemical structure and biological properties.

7) Final therapeutic evaluation in large numbers of cancer patients.

Such a complete program is, of course, national in size and beyond the resources available to any one institution. The chemotherapeutic effort is being implemented partly through resources now extant and through close collaboration with other groups interested in the chemotherapy of cancer. The Cancer Chemotherapy National Service Center facilitates procurement of desired agents, provides additional screening, additional clinical participation, and helps to prevent unintentional or undesirable duplication of effort.

Objective criteria of drug effect on various types of neoplastic diseases are being defined. Leukemias present relatively little difficulty in this regard, other than an agreement among the parties concerned as to uniform standards for complete and partial remissions, respectively, as

instigated by the National Cancer Institute. Cutaneous metastases and other superficial lesions may be measured accurately, and discrete pulmonary metastases may also be followed in serial roentgenograms with reasonable facility. Those neoplasms that elaborate pharmacologically active and chemically measurable substances or influence the excretion of metabolites must be considered on their own merits. As noted, change in excretion of chorionic gonadotrophin by choriocarcinomas seems to be a reliable index of growth or regression of that particular cancer, while the output of adrenocorticoids may be suppressed without obvious effect on the growth of adrenal carcinomas. Detailed study of the growth of individual cutaneous metastases shows great variation in their behavior. Different lesions in the same patient may progress, regress, or remain stationary simultaneously.

Experience with methotrexate and 6-mercaptopurine in the treatment of acute leukemias at the National Cancer Institute is not materially different from that reported by other groups. Methods for measuring these compounds in body fluids are being perfected. A different drug, 6-azauracil, provided through the courtesy of Dr. A. D. Welch, of Yale University, has induced remissions in about one third of leukemic patients whose disease is no longer influenced by treatment with methotrexate or 6-mercaptopurine. Although 6-azauracil is relatively nontoxic for laboratory species, it produces neurological signs in man that disappear promptly on withdrawal of the drug.

Methotrexate produces depression of bone marrow and ulceration of the oral and intestinal mucosae as manifestations of toxicity. Changes in the growing hair roots, which antedate more serious evidence of drug toxicity, can be correlated with the dosage of methotrexate and some other chemotherapeutic agents. Similar changes in the growing hair root are produced by X irradiation. Good quantitative correlation between intensity of effect and dosage of ionizing rays provides a practical index of radiation exposure of the hairy surfaces of the body. Studies of this type can be carried out only in man, since his hair roots represent a spectrum of growth phases, whereas the hairs of laboratory animals are either all resting or all growing at the same time.

A riboflavine analogue that clearly retarded the growth of two experimental cancers was generously provided for clinical trial by the Upjohn Company at the request of the National Cancer Institute. No beneficial effects were obtained in patients with advanced disseminated cancers, nor was it possible to produce riboflavine deficiency. Significant differences were demonstrated in the metabolites of the drug excreted in the urine by rats and by humans, which may account for the differences in the activity against cancers in the same species. The prototype compound being rather poorly absorbed, a new drug was made that could be given parenterally. This compound was rapidly metabolized and excreted. The metabolites demonstrated little or no antiriboflavine activity, and patients receiving the parenteral preparation demonstrated neither riboflavine deficiency nor any effects on the growth of their

cancers. The future of the antiriboflavine approach to cancer chemotherapy rests upon availability of more potent biological antagonists of riboflavine activity that will produce deficiency in man.

During the course of the antiriboflavine study, a patient who had received a fluorescent analogue came to necropsy. The metastatic cancers fluoresced brilliantly under ultraviolet light. Good detective work established that the fluorescence was due to earlier treatment with tetracycline rather than to administration of the antiriboflavine compound. Laboratory investigation has now established that tetracycline and some related compounds are retained by a variety of experimental cancers and by newly formed bone. No biological consequences have been noted. Apparently the drug itself, rather than a derivative, is bound to some protoplasmic constituent, and additional research may define some method of exploiting this finding for the benefit of the cancerous patient.

Clinical investigation is materially aided by the ability of laboratory investigators to define exact dose-response relationships of anticancer agents. The methods permit comparison of the relative efficacies of different compounds against experimental cancers. The antineoplastic effectiveness of a drug need not be a fixed characteristic. It may be altered by factors pertaining to the host and to the tumor as well as by the method by which the drug is used. The effectiveness of drug action against tumor can be increased without increasing its toxic action. These findings have been made possible through the use of quantitative methods of inhibition analysis, which also provide one method of integrating biological and biochemical investigations.

The best chemotherapeutic responses terminate with recurrence of cancer in a form that seldom yields in any marked degree to treatment with the same initially effective agent. The occurrence of drug resistance among mouse leukemias was reported almost simultaneously from the National Cancer Institute and the Sloan-Kettering Institute during 1949, and it now appears that transformations to resistance occur rather commonly among acute lymphocytic leukemias of the mouse. The change is stable, irreversible, and heritable, and reversion to the drug-sensitive state does not occur. The pattern of resistance to some of the drugs resembles that developing in bacteria to penicillin. Experimental evidence favors the view that the variant cells arise by spontaneous mutation, which occurs constantly in the population of leukemic cells, the metabolic antagonist acting as a selective agent in the propagation of the variant form. The biochemical mechanism of resistance is not known. The most feasible approach to the problem of resistance seems to be an attempt to suppress the selection of spontaneous transformations through the use of two or more agents acting independently, as in the treatment of bacterial infection. Thus, doubly resistant mutants have a negligible probability of emerging in a sensitive tumor or bacterial population in the presence of two or more effective agents that exhibit different mechanisms of action. The consecutive administration of

two antimetabolites, such as methotrexate and 8-azaguanine, in appropriate doses and with appropriate timing is more effective in increasing survival of leukemic mice than administration singly, but concurrent administration causes a striking potentiation of the effect, and some of the mice show no evidence of disease. Clinical investigations of leukemia therapy based on these principles are in progress. A considerable variety of experimental leukemias and related diseases is now available for therapeutic research. These include transplantable plasmacytomas that faithfully reproduce the major features of their human counterpart, including the production of myeloma proteins.

Still another approach to the treatment of cancer is the use of filterable viruses that produce comparatively minor disease in man. The basic observation that HeLa cell cultures were largely destroyed by adenoviruses was made by a scientist in the National Institute of Allergy and Infectious Diseases, and a fruitful collaboration between members of the two institutes has been in progress for some time. Since HeLa cells originated from an epidermoid carcinoma of the cervix, solutions containing adenoviruses have been injected directly into cervical cancers of patients whose lesions are far advanced. No noteworthy effects occur if the individual possesses specific antibodies against the type of virus employed, but the patient whose blood serum contains no demonstrable type-specific antibodies soon excavates a part of the site injected and extrudes necrotic material into the vagina. The response is limited and is not therapeutically useful at this time. The antibody response in some women is so rapid as to suggest a type of reaction similar to that observed in patients who receive "booster" injections of tetanus toxoid some years after primary immunization. The results encourage further exploration of the use of viruses as cancerocidal agents. It may be practical to enhance the action already demonstrated for adenoviruses, and other filterable viruses should be explored for similar properties.

This brief recital of accomplishments during the first twenty years of the National Cancer Institute is far from complete, and other noteworthy achievements of the past and present necessarily have had to be omitted. Changing emphasis results from progress in research, giving a high degree of flexibility to the program. So active are the programs that a story of this type told one year hence might be oriented in an entirely different way, and certainly this one reflects the personal viewpoints of its writer.

The National Cancer Institute has come a long way since 1937. It is larger. The areas of research are more diverse. The staff is distributed among three buildings on the Bethesda campus. Knotty problems of communication torment all of us and tend to compartmentalize the activities. These are the consequences of bigness. They are not insuperable problems, and decentralization of responsibility with commensurate authority, accomplished a year ago, has been a step in the right direction.

The problems that cancer poses are intricate indeed. Probably no individual nor any group of persons can define that single approach to the

control of cancer that holds the greatest promise of success at this time. The more one learns about neoplastic diseases, the more dependent one becomes on advances in basic science. We are unlikely to accomplish our objective by studying cancer alone. Progress has been most rapid in scientific research when imaginative, talented, technically competent, intellectually curious, and, above all, sincerely interested investigators are encouraged to search for new facts beyond the curtains that limit our knowledge and to pool their specialized resources and skills on a basis of mutual interest and respect. The ultimate usefulness of any one fact may not be apparent immediately, but acquisition of enough facts will, in time, solve this problem.

The Research Grants Branch of the National Cancer Institute

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History and Philosophy

IN the medical and scientific atmosphere preceding the enactment of the National Cancer Institute Act in 1937, there was a mixture of emotional and professional attitudes that was both encouraging and discouraging. It is probably fair to say that aside from those who engaged in cancer research, the majority of professional medical men had little hope that the mysteries of the disease would ever be understood. Research scientists, however, including some practicing physicians, held to the hope that if more could be learned about the principles of abnormal growth, some of the etiologic agents, and means for earlier diagnosis, there eventually would be available to the physician more effective measures for controlling the disease.

The major portion of the funds available for fundamental cancer research previous to 1937 came from endowments or trust funds set up by public-spirited citizens, often from families that had been affected in a personal way by the disease. In 1922, the Federal Government through the Public Health Service had launched a small research program. The funds had been gradually increased over the years but still were not large.

In an article published by *Fortune Magazine* in April, 1937, based on their own survey, the authors estimated that the total amount available in the United States for cancer research was around $700,000 annually. Among the chief sources of the funds, aside from those of the Public Health Service, they listed the International Cancer Research Foundation, Philadelphia, the Crocker Cancer Research Fund, New York City, the Anna Fuller Fund, New Haven, Connecticut, the Jonathan Bowman Fund at the University of Wisconsin, the Henry Rutherford Fund at the Rockefeller Institute, New York City, the C. P. Huntington Fund (used at New York's Memorial Hospital), the Bondy Fund at Columbia University, New York City, the Chas. F. Spang Foundation, the income from which went to the University of Pittsburgh Medical School, and the Mack Memorial Fund, part of which was for cancer research and which went to the University of California. There were a number of other small funds, the authors said, but none that exceeded $100,000.

The passage of the National Cancer Institute Act in 1937 was the

beginning of the movement by the Federal Government to put more money into cancer research. In that same year, the establishment of the Jane Coffin Childs Memorial Fund for Medical Research, a large trust fund, at Yale University, was another evidence of the increased effort by private funds. Both public and private efforts have grown almost continuously since that time. In 1944 the American Society for the Control of Cancer was reorganized as the American Cancer Society. The new organization undertook a national fund-raising program to finance research as well as to expand its educational and other activities. The phenomenal growth of the organization and its success in raising ever-increasing sums for research, education, and control activities attest to the genuine desire of the American people to provide voluntary dollars to conquer cancer.

Further evidence of this is found in the support given to the Damon Runyon Memorial Fund for Cancer Research established in honor of Mr. Damon Runyon, a prominent newspaper man, who died of cancer at an early age. In addition to these two, private funds have provided numerous other gifts, trusts, and endowments in the last two decades to aid cancer research.

Since the close of World War II, the Federal Government has provided funds for a greatly expanded cancer program, a large part of which has consisted of grant-supported research at institutions all over the United States and a few in foreign countries.

Industry has to a small degree in recent years begun to recognize the hazards that its processes may create for its workers, for people living in its environs, or for persons using its products. It has fostered research and the establishment of control measures to remove or minimize these hazards.

State and local governments have likewise reflected the interest of the people by appropriations for research, diagnosis, treatment, and prevention of cancer.

Simultaneously with the increasing availability of funds for cancer research, there has been an increase in the opportunities to use these funds. Developments in medical research have brought new courage and hope to the older cancer investigator and challenging opportunities to the newer recruits. The amount of work that each can do and the power to tackle previously unapproachable problems have been enormously increased by the development of new instruments and techniques and the availability of trained technicians and more adequate space. All of these adjuncts to research, however, add to its cost.

With the expansion of research on cancer and means for aiding it, the question is sometimes asked whether it would not be more efficient and effective to combine all sources of aid into one agency with one set of advisors. This concept of efficiency and simplification fails to consider the dangers of the concentration of power in the hands of a relatively small group and the proportionate loss of flexibility as the size of an organization grows. It makes the erroneous assumption that some in-

dividual, or group of individuals, is omniscient in determining which aspects of research are more important and the extent to which they should receive research support. It overlooks, also, that very important characteristic of Western Civilization which stresses the significance of the individual, whether it be how he shall do research or how he shall provide aid to those who do research. It is important to research that there shall continue to be multiple sources of aid and that the investigator shall have recourse to another reviewing body if the worth of his proposal is not recognized by one or more organizations he approaches for support. One has only to review the history of medicine and science to derive numerous examples of ideas now fully accepted that, when they were proposed, were not accepted by a large segment of the learned men of the time.

While there is room for individual or group initiative and freedom for the operation of private enterprise, it is important to have voluntary communication and cooperation in working toward the common goal. The National Cancer Institute has welcomed, encouraged, and learned from its companion organizations. It has fostered close relationships and sought to integrate its efforts with those of other agencies with like purposes. This liaison is effected, formally, through exchange of staff representatives to advisory committees and councils and, informally, through continual staff interchange of information and through cooperation in the development and support of programs of mutual interest. This avoids unknowing duplication of effort and may make joint financing of research possible, which one agency could not or would not finance alone.

The philosophy of philanthropy is an engaging subject, which cannot be discussed in detail here but which has many facets that are pertinent to providing aid for research to alleviate the ills of mankind. The provider and the recipient of aid need to have as clear an understanding as possible of what each expects of the other. If one thinks he is buying or selling such a product as a cure for cancer, a contract that will protect each party is almost essential. If, on the other hand, the giver is providing funds to enable the user to direct his efforts in the best way he knows toward a goal that has been agreed upon, the grant-in-aid amounts to an act of faith. In such cases, both parties recognize that the goal may not be achieved in a specified time. Few situations are so clear cut that they fall into one or the other type. Yet the emphasis toward one or the other type will largely influence the conditions under which aid is given and accepted. The degree of freedom allowed to the recipient in the use of funds is likely to be in proportion to the degree of confidence the giver has in the integrity, wisdom, and competence of the recipient. This may be almost inversely proportional to the number of restrictions that are designed to retain some kind of control by the giver. The strings may be so few that misuse is possible. Or they may be so numerous and confusing as to enmesh the recipient in a web that prevents accomplishment of the aims which led to the gift.

Years ago, the Rockefeller Foundation for Medical Research set an example among fund-granting agencies by providing assured support for

a long term (ten years or more) for selected persons of recognized ability and integrity. A minimum of restrictive conditions was placed on the use of these grants. At the other extreme was a foundation that gave small amounts of money in annually renewable grants for highly specific projects which were defined in detail. The recipient was required to make a quarterly report of progress before the next quarterly payment on the grant would be made.

During the past few years we have heard increasing discussion on whether project grants are an effective way to support research. Some agencies have devised other types of support to meet special needs. Since the research-grants program of the National Cancer Institute consists primarily of project grants, some consideration of this question is included here.

The practice of supporting research through project grants began to be widely followed as funds for research became increasingly available in the last two decades. Grants usually were awarded for specific projects based on a specified plan submitted by the applicant, and support frequently was recommended for only one year. This arrangement had a number of disadvantages. The applicant was more or less obligated to follow his proposed plan even though information obtained later indicated that some other approach might be more successful. The budget originally submitted with the application could not be changed without authorization of the granting agency. Because there was little security or assurance of continuity of support, it was difficult to employ competent personnel to work on projects. To obtain continuing support, investigators felt it was necessary to investigate rather narrowly defined problems that could be completed in a comparatively short time.

During the past ten years many changes have been made in the philosophy and practice of project grants as administered by the National Cancer Institute and the National Institutes of Health. The specific plan proposed by the applicant primarily constitutes a basis for the reviewers to determine whether the applicant is fully informed and is competent to carry on research in his selected field of investigation. Each grantee is advised that he is free to change his research plan any time this appears desirable. With a few minor exceptions, the grantee may rearrange his budget as his needs change during the course of the investigation. For the most part, support is recommended for periods of three to five years. This makes it possible for the investigator to obtain more competent personnel and to undertake projects of longer duration and greater importance. Also, a project may be broadly defined to constitute either the specific research plan or the total research program of a single investigator or the program of a group of investigators, if this appears desirable. A research project that embraces the total or partial program of one or many investigators is more easily handled if it is within the competence of one Study Section and one Council.

Thus, the administration of the research-grant program has been designed and modified, as needed, to support competent investigators,

to sustain a broad concept of relevance to disease, and to give the investigator maximum freedom. Much has been said and written that is critical of the system of project grants. In general the criticism is more valid with respect to the principles that the critics attribute to such grants than to current administrative practice. In form, grants have been given for the execution of designated tasks; in practice, awards have been made on the basis of the evaluation of the investigator and his ideas rather than on the plan that he imposed upon himself.

Operational Aspects

From the time the National Cancer Institute was established, in August, 1937, until the end of World War II, the funds available and the number of applications for research grants were comparatively small. During this time, applications were evaluated entirely by the National Advisory Cancer Council with the assistance of individual scientists when it was desirable in special cases. The membership of the Council consisted of six scientists and physicians representing the scientific and medical fields pertinent to cancer research. During this period the Council could adequately evaluate all applications by meeting for one day, four times annually.

As the number of applications and the funds available for research grants increased markedly from 1946 to 1949, it became apparent that it soon would be utterly impossible for a single small group to evaluate all applications. In 1946 the Division of Research Grants of the National Institutes of Health established a system of Study Sections, in specific scientific and research fields, to make a preliminary review of applications and to recommend appropriate action to the National Advisory Health Council. Gradually the responsibility of the Study Sections was extended to serve all Councils and Institutes. The National Advisory Cancer Council began to receive this type of expert assistance in 1949.

There are now some twenty-seven Study Sections covering a wide area from Allergy and Immunology, Behavioral Sciences, Biochemistry, Biophysics and Biophysical Chemistry, Cancer Chemotherapy, and Cardiovascular to Sensory Diseases and Surgery. Most of these Study Sections assist the National Advisory Cancer Council by making recommendations in regard to applications in their respective disciplines, which have been assigned to the National Cancer Institute. A Study Section consists of ten to eighteen scientists drawn from universities, hospitals, and research institutions all over the country. The membership of the Study Sections is rotated so that in general each member serves four years.

The deadlines for receipt of new applications are July 1, November 1, and March 1. The Study Sections meet two to four days each usually in September, January, and April. The Cancer Council meets three or four days in November, March, and June.

Applications are received by the Division of Research Grants, logged in, given an accession number, and assigned to an appropriate Study Section and Institute. For example, if an application is concerned with

studies of tumors of endocrine glands in animals, it would be assigned to the Endocrinology Study Section and to the National Cancer Institute. Copies of the application are distributed to members of the Study Sections several weeks prior to the meetings.

At the meetings of the Sections, each proposal is discussed in detail with special consideration given to the general competence of the applicant, his background and experience for the project proposed, the merits and promise of the proposal, the relation of the funds requested to the proposed work, and the facilities that are available. As a result of this discussion, a specific recommendation is made and transmitted to the appropriate National Advisory Council and Institute. Because the funds available each year are rarely sufficient to support all recommended projects, they must be placed in some order in relation to their scientific promise and pertinence to cancer research. This order also is recommended by the Study Sections.

The recommendations of the Study Sections are transmitted to the Research Grants Branch of the National Cancer Institute, which distributes them, with copies of the applications, to members of the National Advisory Cancer Council. Members of the Council are requested to return preliminary votes on all applications prior to the meeting. For the most part the Council concurs with the recommendations of the Sections. However, if a member of the Council has detailed personal knowledge or any questions regarding an applicant or a proposal, he may request that an application be brought up for special discussion at the Council meeting. It should be emphasized that this does not apply to applications from a Council member's own institution. In both the Council and the Study Sections, any member of the group leaves the room during the time that an application from his own institution or one in which he may have any personal interest is under consideration.

The Council consists of fifteen members, twelve of whom, like Study Section members, are appointed by the Surgeon General. Three are members *ex officio*. Approximately half of them are scientists from universities, hospitals, and research institutions in various parts of the country. The remaining members are laymen who are leaders in philanthropic or civic affairs or some other public activity. The membership is rotated so that in general each member serves four years. Representatives of organizations, such as the American Cancer Society, Atomic Energy Commission, Department of Defense, National Science Foundation, and Veterans Administration are invited to Council meetings so that excellent liaison is maintained with related activities in these agencies.

At the Council meeting, attention is given primarily to applications about which questions have been raised, matters of policy, and questions of program development. Whereas a Study Section sees only a segment of the cancer research effort, the Council sees the total program. For the most part, the Study Section is concerned with the scientific evaluation of the applicant and the project. The Council directs more attention to questions of policy, although it is impossible and perhaps undesirable to

insist on a complete separation of these responsibilities. Even though a project may not be of great scientific merit, the Council may feel it should be supported on the basis of encouraging and stimulating research in a field where little is being done or in a particular institution or geographical area where the opportunity to develop research is promising. In proposals involving clinical follow-up studies, the question sometimes arises as to how much of this type of work should be the responsibility of any good hospital and how much should be supported with funds for cancer research. This decision is primarily a responsibility of the Council. Grants may be awarded to institutions in foreign countries if, for scientific reasons, the work can best be done outside of the United States. Scientific reasons may consist of the outstanding competence of an investigator, the nature of the problem, or the availability of facilities, special equipment, or research material not available in this country. The Council gives special consideration to these questions.

The actions of the Council take the form of recommendations to the Surgeon General. The Surgeon General may award research grants only when they have been recommended by a Council. However, he has the prerogative of refusing, for just cause, to award a grant that has been recommended by a Council. With rare exceptions, the Surgeon General has accepted the recommendations of the Councils. The recommendation to the Surgeon General for the award of a grant to an institution outside of the United States must be accompanied by a special justification. A few other problems of this kind with unusual implications are specifically brought to his attention.

The need for some mechanism for review and evaluation of applications as described above is readily apparent when it is realized that the Division of Research Grants of the National Institutes of Health receives approximately 9,000 research-grant applications annually. More than 1,000 of them are assigned to the National Cancer Institute for final review by the Cancer Council. During the calendar year 1956, for example, the Council reviewed 1,137 applications requesting a total of 19.3 million dollars and recommended the award of 1,014 grants for a total of 16.6 million. Such a task would be impossible without the assistance of the scientific community at large as expressed through the contributions of the several hundred highly competent scientists who serve on Study Sections.

The selection of research proposals to be supported by funds of the National Cancer Institute would be greatly simplified were it possible to give, in operational terms, a concise, workable and exclusive definition of the area of medical and biological research that would be clearly pertinent to cancer. Were cancer a single disease of well-defined cause, it would be possible with some confidence to distinguish those studies that are pertinent from those that are remote. Unfortunately, for the present at least, cancer must be regarded as a group of many diseases with many indeterminate causes.

In this situation, almost all major areas of medical or biological research may be of immediate importance to the control of cancer in man. Any

study, which advances our knowledge of the physiology of the cell, and the factors that control cell multiplication and differentiation, and any new knowledge of the response of cells to radiations, chemicals, hormones or viruses, is pertinent.

For example, it may be that the best way to find out how cancers become independent of the normal growth controls will be through studies on plants and plant tissues where endocrinologic factors appear to be less complicated and more readily subject to critical analysis. Perhaps studies in cellular physiology or tissue culture will open the way to an understanding of how cells are held together and how they move and thus explain the invasiveness of cancer cells. Very likely the action of compounds that inhibit cell division can be studied best on nonmammalian cells, which are particularly suited for investigations of this type. Similarly, the mechanism of action of many compounds that induce or inhibit cancer can be approached readily through investigations on bacteria, eggs of marine animals, cells in tissue culture, and similar biological materials that have little apparent relation to cancer in man. Again, an understanding of genetic principles and of the way in which chromosomes show their influence may be most easily established with protozoa, bacteria, fungi, insects, or mice. Therefore, in the present state of knowledge, it is less a matter of scientific judgment than scientific intuition to decide whether a particular study bears immediately or remotely on the problem of cancer.

Since the understanding and control of many other types of disease depend upon similar knowledge of the fundamental characteristics of living matter and the manner in which it grows and reproduces itself, there is need for encouragement and support of all research that contributes to an understanding of life processes whether or not it is immediately applicable to a specific health problem. Only through such continuing efforts to understand nature can there come the constant replenishment of the pool of basic concepts from which flow the streams of knowledge that can be applied to specific problems of disease control. All agencies concerned with problems of health and welfare have a responsibility to foster the development of the basic understanding on which the success of their more specific missions and objectives rest. The interrelatedness and interdependence of nearly all fields of scientific and medical knowledge is immediately apparent to those who attempt to solve problems, but it is often overlooked by those whose range of vision is narrower and whose focus is restricted to a specific form of disease.

Furthermore, developments in research constantly emphasize that it is rarely possible to separate the acquisition of basic knowledge from its application. Attempts to apply present knowledge frequently drive the physician or applied scientist to a search for more fundamental facts and concepts. And the pure scientist is constantly making discoveries for which he or someone else sooner or later finds an application that will improve the health and welfare of man.

There is a place and an obligation, therefore, for basic science research

in the programs of organizations oriented to disease control. In an organization like the National Cancer Institute, the extent to which funds for cancer research can appropriately be used to support related studies of normal cells, tissues, and organs must be constantly examined by the staff and by the advisory bodies.

The most important ingredient in any research effort is the thinking capacity of the investigator as shown by his power to generate new ideas, to select significant problems, to design experiments adequate to test hypotheses, to carry them out, and to evaluate and interpret objectively the results obtained. Applications for grants-in-aid, together with the evidence from previous work done, are intended to provide means for assessing these qualities in the investigator. In all grants, there is tacit assumption that if an investigator is worthy of support at all, he must be a person of sound scientific integrity who is capable of determining, as his work progresses, what modifications of direction and methods will best foster the aims for which he sought research aid.

For these and similar reasons, each investigator is left completely free to select for himself the areas of research that he feels are most promising and in which he is most competent. Each investigator is free to frame his problems in the way he sees them and to design his experiments in the way that seems best to him. Therefore, the ideas behind the projects that have been supported have come from the investigators conducting the projects. The answer to the question "what is cancer research?" has not been a decision of any one small group but rather has resulted from the integration of the judgments of several thousand working scientists who believed they had something to contribute to the cancer problem.

In some respects this may be interpreted as a *laissez-faire* policy. It is not, however, a random policy simply because the progress of science is not random. It has a strong sense of direction, intuitive but compelling. A discovery by one investigator influences the viewpoints and approaches of many investigators in many fields of study. Thus the thoughts of independent investigators mold each other's emerging ideas and a consensus develops that is the real architect of the pattern of cancer research at any time.

It is true, of course, that the recommendations of the National Advisory Cancer Council and the Study Sections and the decisions of the Surgeon General might appreciably modify the pattern of cancer research by failing to provide support for projects in certain areas that may appear to be less promising or less pertinent to cancer. However, the system of review and approval utilized by the Public Health Service includes several self-correcting mechanisms that tend to prevent this from occurring to an undesirable degree.

Each request for support is reviewed by both a Study Section and the Council. It is unlikely that an appreciable number of the members of both groups would agree that a particular study or field of investigation would contribute little to cancer research unless this opinion was generally accepted and did in effect represent the consensus of scientists in general.

The membership of these scientific advisory groups is gradually rotated so that the viewpoints of one or a few individuals are not likely to prevail for long unless they are based on sound principles and are in agreement with the thinking of the scientific community. Finally, in the most unlikely event that neither the Council nor the Study Section recognized the value of a particular proposal, there are several other sources of support for cancer research through which the applicant may obtain evaluation by a separate and independent group.

One of the most important problems concerned with the support of cancer research is the problem of maintaining a balanced but aggressive program. There must be some suitable relationship between the amount of support for research training (fellowships and training grants) and the amount of support for research *per se*. The research training activities of the National Cancer Institute are discussed elsewhere in this report. Within the research grant program there must be some determination, in a general way at least, of the proportion of available funds that should be used to support each aspect of cancer research, such as endocrinology, virology, metabolism, biochemistry, and others.

To a large extent, this determination is made by the scientific community as a whole, much as described previously. The most competent investigators usually are the first to note the particularly promising areas within their general field of interest. Since they are especially competent, they are likely to receive support for their work. In this way interest and activity in a particular area of cancer research waxes and wanes in proportion to the promise and importance of a specific area of investigation. In other words, cancer research, like science in general, has a built-in coordinating mechanism dependent primarily on the support of high-caliber investigations.

As might be expected, this automatic coordinating mechanism alone is not completely adequate to meet the needs of a large and voluntary cancer research program. There are two types of research areas, in particular, demanding the utmost in intelligent programming. One type is exemplified by fields, such as cancer chemotherapy, endocrinology, and steroid biochemistry, the results of which are directly applicable to cancer in man. In these cases, the general problem is to bring to the cancer patient, as soon as possible, the results of the laboratory investigations. During the past few years, Congress has made available increased funds specifically for research in these areas. As long as these areas are operationally defined in a broad sense and as long as adequate funds are available, most investigators would agree that all meritorious projects in these fields should be supported. Under these circumstances, however, care must be exercised that the allocation of a disproportionate amount of support to a specific aspect of cancer research does not distort the program and divert facilities, manpower, and attention from more fundamental areas of investigation, which must of necessity serve as the basis for any practical or applied developments. That is, too many investigators may become so interested in harvesting the fruit that too few

would take time to plant more trees. However, this problem also has a built-in self-correcting mechanism, based again on the consensus of the scientific community. When a practical aspect of a problem is pushed beyond the available necessary basic information, results diminish and enthusiasm wanes. Competent scientists look for more productive areas of investigation, and this attitude is reflected in the recommendations of the reviewing bodies of the National Cancer Institute. Nevertheless, a continual effort is made to be alert to the dangers of special emphasis, which may be premature, poorly conceived or executed, and which may interfere, at least temporarily, with more productive efforts.

The other type of investigation, which requires attention to programming and which is much more difficult to develop, is the research area in which relatively little is being done. For example, the National Cancer Institute has been supporting only two investigations on a highly theoretical study of the electron structure and density of organic chemical compounds. This is one type of study that is being supported in a foreign country, because so little is being done about it in the United States. This particular investigation is directed toward finding out why some organic chemical compounds induce cancer, whereas other closely related compounds have no such effect. However, most of the biologically important compounds except water and minerals are organic, and extensive development of this field might be as important to cancer research as the Einstein theory of relativity has been to nuclear energy. On the other hand, there probably are less than a dozen investigators in the world who are experts in this field. Development of this area would involve the long, slow process of selecting and training young investigators with the ability required to work successfully in this highly specialized field. Finally, there is no assurance that the results of this expansion would make any important contribution to cancer research. In making the difficult decision on a question of this type, the National Cancer Institute is again guided by the consensus of the scientific community as expressed through the members of the Council and Study Sections and through the extent of interest of the scientific community at large.

Research Training Grants

The research training grant program is the newest of the added responsibilities of the Research Grants Branch. It began in the current fiscal year when 1.2 million dollars were specifically allocated for this purpose.

During the past ten years there has been an increasing realization on the part of Government and of the scientific community in general of the greater need for training more young investigators. It is true that sizable funds have been available for predoctoral and postdoctoral research fellowships and that a large element of research training is involved in the case of many junior personnel who are working on research grants. However, it was felt that both types of support lacked certain

important advantages to fulfill completely the need for additional research training opportunities.

With regard to fellowships, it is up to the individual trainee to apply for and obtain his own support to work in a laboratory of his choice. This arrangement requires that plans be made many months in advance and involves the delays and discouragement that may occur under these circumstances, frequently through no fault of the trainee. Also, fellowships bear only a part of the total cost of the training. Most of the cost of supplies, equipment, and training personnel must be absorbed by the institution or laboratory where the fellow works. The trainee is subject to a good deal of insecurity, because fellowships are awarded for only one or two years and further support is contingent upon the decisions of evaluating groups who cannot be completely familiar with the local situation. Some of these difficulties are less applicable to junior investigators employed on research grants. However, the responsible investigator can use only a limited part of his funds in training inexperienced personnel without reducing the productivity of his project and jeopardizing his support for the future.

The purpose of research training grants is to enable qualified academic research centers to expand their research training programs primarily at the predoctoral, postdoctoral, and more advanced levels. It should be emphasized that this training program is intended to supplement and augment, not replace, present programs maintained by the institution. It is intended, also, that it supplement and not replace sources of support for junior and senior research personnel who may presently be obtaining research experience through fellowships or as employees on research grants. The emphasis in this program is to be on the provision of research training opportunities. Any specific research results will occur only as a by-product.

A training program may represent primarily the fields of interest and competence of one or two senior investigators or it may encompass the combined efforts of one or more departments. The choice of candidates, the stipend levels, and the content and organization of the training program are left entirely up to the institution and the program director, subject only to a review of the plans before a grant is awarded and when future grants are requested.

Applications are submitted in much the same way as for research grants. If the application is recommended, a grant is made to the institution for that specific program. In addition to trainee stipends, applicants may request funds for supplies, equipment, travel, and for salaries for training personnel, where this seems necessary. Budgets for these grants have the same flexibility as those for research grants except that funds budgeted for trainee stipends may not be transferred to any other category. The National Advisory Cancer Council is of the opinion that to obtain maximum effectiveness, support for research training programs should be recommended for five years at a time. During this initial period, however, requests have greatly exceeded available funds, and considerable attention

is being given to the problem of formulating general policies to guide the program in the future. For these reasons, the initial awards were recommended for only three years.

It is anticipated that this program will expand and improve the opportunities for research training. If it is mutually decided that a research trainee should work with a particular investigator or in a particular laboratory that has a training grant, arrangements usually can be made quite promptly. The selection of the trainee and of his particular research training program is a responsibility of the program director who ordinarily will have an intimate knowledge of the ability and interests of the individual as well as of the facilities and type of training that can be provided in that particular laboratory. The stipend can be adjusted as may be required by the needs of the individual and the environment in which he is working. Usually the trainee can be given assurance of future support for a reasonable time. If requested, funds may be provided for supplies, equipment, and travel. Although there appears to be general agreement that it is particularly important for young research personnel to attend scientific meetings, most fellowships provide little or no funds for this purpose. It is intended that these grants bear the major cost of the expanded research training opportunities. Because funds have been limited, however, support for staff salaries has been recommended only in those instances in which it was clearly essential to the expansion of research training opportunities.

During the first year of this program, the Council established some basic concepts as guides to plans for the future. In regard to the eligibility of institutions to receive research training grants, it is felt that no rigid specification of eligibility should be adopted but that preference should be given to institutions that will provide research training for postdoctoral researchers and for predoctoral graduate students, medical graduates, and medical students who take time off from their academic courses. Other areas of lesser preference might include institutions that give training in research procedures to secondary-school science teachers, undergraduate college students, medical and research technicians, and precollege students.

In regard to types of research training programs, it has been agreed that no specific types should be excluded. Of course, programs designed primarily for training other than research, and those that are primarily research projects in which the training aspects are incidental, should seek other types of support. Also, no rigid restrictions have been established as to the breadth of a program whether departmental or interdepartmental, disciplinary or interdisciplinary.

With regard to the size of research training grants, it is considered generally desirable to encourage research training in as many centers as can offer sound training programs. Therefore, the size of grants has been kept to as low a figure as possible consistent with sound training operations. Supplemental funds may be requested for those programs that develop well and have an opportunity to train larger numbers of qualified candi-

dates than provided for by the original grant. Also, some preference has been given to proposals with minimum requirements for staff salaries, equipment, and renovation, provided these are for programs where high-quality training will be given and in areas where new research manpower is especially needed. However, this does not exclude support of excellent training centers where additional staff, equipment, and facilities are necessary for an expanded research training program.

It has not been considered feasible thus far to recommend the award of research training grants to support the general training activities of graduate departments in the basic and preclinical sciences no matter how meritorious these may be. Every graduate student in departments, such as anatomy, biochemistry, physiology, and pharmacology may be considered in training for a career in research that may be potentially related to cancer research. To this extent, any expansion of the research training activities of such departments might be considered as eligible for support from cancer research training grants. Thus far, however, support has been recommended primarily for those programs that are, relatively, directly pertinent to cancer research, and, it is felt that for the present at least, the support of the regular research training activities of graduate students must continue to be a responsibility of the academic institutions or should be financed by noncategorical research training funds.

Research Fellowships

Table 1 summarizes the number of research fellowships awarded and the funds expended for fellowships by the National Cancer Institute during each fiscal year from 1947 to 1956. The number of awards indicated in the table refer to the number of individuals who received support during each year. Since some individuals received support for two or three years, the table does not indicate the total number of individuals who received support.

The postdoctoral and predoctoral fellowships are the conventional type of award in these categories with which most people are familiar and they require no further comment here.

Special fellowships are awarded to qualified applicants who have demonstrated unusual competence in research or require specialized training for a specific problem. In general, the recipients of these awards are senior to and have had more research experience than the usual postdoctoral fellow. In order to fulfill special needs, the provisions of the special fellowships in regard to stipends and duration of support have been kept as flexible as possible.

As indicated in table 1, a new program of student fellowships was begun in 1956. This is a coordinated activity of all Institutes of the National Institutes of Health and is financed cooperatively. The fellowships are in the form of grants awarded to acceptable medical, dental, nursing, and public health schools upon approval of an application submitted by the dean or his authorized representative. The amount of each grant is based upon a certain number of units, in the amount of $600 each, plus indirect

TABLE 1.—*Summary of fellowships awarded by the National Cancer Institute 1947–56*

Fiscal year	Postdoctoral		Predoctoral		Special		Student		Total	
	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds
1956	92	$375, 420	118	$267, 108	12	$54, 147	256	$110, 624	478	$849, 923*
1955	140	569, 267	102	250, 318	10	41, 140	—	—	252	860, 725
1954	155	690, 582	9	9, 688	13	49, 674	—	—	177	749, 944
1953	103	460, 281	49	122, 514	10	41, 667	—	—	162	624, 462
1952	58	246, 929	96	230, 831	5	21, 025	—	—	159	498, 785
1951	91	278, 179	79	170, 820	9	36, 571	—	—	179	485, 570
1950	85	296, 959	53	107, 204	17	89, 216	—	—	155	493, 379
1949	83	276, 871	51	103, 532	25	108, 929	—	—	159	489, 332
1948	54	182, 589	43	87, 278	9	28, 479	—	—	106	298, 346
1947	15	†	28	†	2	†	—	—	45	77, 821

* Includes $42,624 in incidental fees applicable to awards for fiscal year 1955.
† Fiscal data not available.

costs. This plan has been established with the idea that each unit may provide for part-time research training during the school term or for full-time research training, for two months, during any period when regular curriculum work is not scheduled for the student. Funds also are available for junior and senior students who may wish to take off a year from the regular academic work to obtain research training. The selection of the fellows is left to the institution, which reports at the end of the year the names of the fellows, the amount of funds expended, and a brief description of the research activities of the fellows. The purpose of this program is to make it possible for competent research-oriented students to begin their research experience early in their career and to stimulate and encourage an interest in research on the part of unusually promising students before their professional training has progressed to the point where they do not feel they are in a position to develop a research interest even though they wish to do so.

The most conspicuous change indicated in table 1 is the increase in total funds expended each year for fellowships, from $77,281, in 1947, to $849,923, in 1956. The plateau from 1949 to 1952 is due to the fact that there was no increase in funds available for cancer research fellowships during that period.

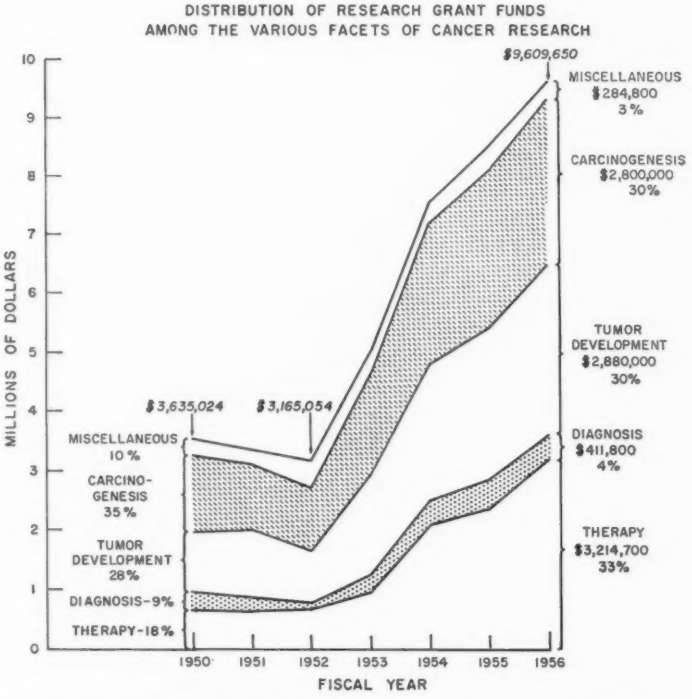
Another point to which attention should be called is the marked reduction in support for predoctoral fellowships in 1953 and 1954. In 1953 questions were raised as to whether predoctoral fellowships could appropriately be supported on a categorical basis and whether such fellowships, to be supported by the Government, should not be awarded through some agency other than the National Institutes of Health. Because of these questions, the predoctoral program was de-emphasized in 1953, since it did not seem wise to make a large number of awards carrying commitments of future support for one or two additional years for which no funds might be available. This prediction materialized in 1954 when the National Institutes of Health were not authorized to support any predoctoral fellowships other than to terminate the few for which commitments already had been made. In 1955 the authority and the funds for support of predoctoral fellowships were restored.

Since the Senior Research Fellowship program began only a year ago perhaps it should be mentioned here, though it is not a part of any Institute activity but is a noncategorical program of the Division of Research Grants. These fellowships are provided to foster additional research in the preclinical sciences by supporting investigators between the completion of postdoctoral training and the time they are eligible for permanent academic appointment. It is essential that these awards not replace departmental funds but that they add to them. Awards are made for five years and are renewable. Approximately fifty fellowships are available annually. They provide a salary for the fellow, partial research support not to exceed $2,000 a year, and indirect costs. Selection is made from nominations submitted by the sponsoring institutions. Grantee institutions may supplement stipends and request additional research support from other sources if they so desire.

Program Analysis

Since 1949 every scientist submitting a research grant application to the National Cancer Institute has been asked to classify his research project indicating the particular facet of cancer research to be explored, the principle discipline or method to be employed, and the anatomical site, if any, which will be of paramount interest in his studies.

Changes in the distribution of research grant funds among the various facets of cancer research during the fiscal years 1950–56 are shown in text-figure 1. In 1950, 403 grants were made totaling 3.6 millions and averaging $9,000 each. By 1956 the annual number of awards had increased to 777 and the total amount granted to 9.6 millions. The average amount of an award rose to $12,250.



TEXT-FIGURE 1.—The total research grant funds and the amounts recommended for different facets of cancer research for each fiscal year from 1950 through 1956.

During this interval, a steadily increasing percentage of available funds was recommended for studies in cancer therapy. In 1950 this facet of the Institute's research grant program received slightly less than 18 percent of the total funds granted. By 1956 it included over 33 percent of the funds approved or 3.2 millions, an amount not quite equal to the total program support six years earlier. While the high level of interest

in this facet in 1954–56 undoubtedly is reflected to some extent in the additional funds made available for chemotherapeutic studies, it should be noted that there is no distinct break between the increasing interest in these years and the spontaneously increasing interest in 1950–53.

The percentage of the total funds available for other facets of the program necessarily decreased over the years of increased interest in therapy. However, the amount of support in terms of dollars increased in all facets. Projects in the field of carcinogenesis were supported at a level of 1.3 millions, in 1950, but received 2.8 millions, in 1956. Studies in tumor development, which were supported in the amount of 1 million in 1950, received 2.9 millions in 1956.

What might be interpreted as a lack of interest in the facet of diagnosis, which received 9 percent of funds, or $324,000 in 1950, and only 4 percent of funds, or $411,000 in 1956, probably is more apparent than real. This modest level of activity undoubtedly reflects the fact that most of the work in this field supported by the National Cancer Institute receives that aid through the Field Investigations and Demonstrations Branch described elsewhere in this issue.

The methods employed in cancer research are classified under forty-six different headings. Therefore, the amounts of money assignable to any one method are relatively small and the changes are somewhat capricious and difficult to interpret. As might be expected, the most heavily supported methods are those of applied chemotherapy, which, in 1956, accounted for 14.7 percent of the awarded funds or 1.4 millions. Assaying and testing chemotherapeutic compounds received 8 percent of 1956 funds, and organic chemistry, largely devoted to the synthesis of chemotherapeutic or potentially chemotherapeutic compounds, received 5.8 percent. No other single method received more than 4.2 percent of the total recommended funds in 1956.

The use of chemotherapeutic methods of all types has expanded concommitantly with the increased interest in cancer therapy. Studies using these methods received 11 percent of total funds in 1950 and 24 percent in 1956.

Support for projects using chemical methods, other than those involved in direct therapeutic research, has shown little change, increasing only slightly from 40 percent of total funds in 1950 to 42 percent in 1956.

Support for studies using biological methods has declined from 31 percent of total funds in 1950 to 24 percent in 1956. Actual support in terms of dollars has, however, more than doubled.

Projects involving the use of physical methods have received a declining percentage of support from 9.0 percent in 1950 to 4.4 percent in 1956. Support in terms of dollars has increased comparatively little in seven years. Unlike all other methods, funds for these studies showed a marked increase in 1952, the low point in support for research grants in recent years. In that year expenditures for experimental megavolt X-ray equipment raised the amount recommended to 13 percent of available funds or $655,000.

Among sites, those most susceptible to treatment by chemotherapeutic means show the greatest concentration of supported research and the most conspicuous changes in emphasis. Studies on blood and lymphatic and hematopoietic tissues received 10.1 percent of total grant funds in 1950. In 1956 they received 27.8 percent of grant funds or about 2.7 millions.

Support for work involving the gastrointestinal tract has declined from a maximum of 11.7 percent of total funds in 1953 to 10.1 percent of the greater total support available in 1956. Within this system the most striking increase was in support for work on the liver, which rose from 5.5 to 6.9 percent in seven years. There was, however, a more than compensatory decrease in support for work on the stomach, from 4.8 to 1.0 percent of total funds. There was little change in the emphasis placed on studies on the oral cavity, esophagus, intestines, rectum, colon, and pancreas.

The urogenital system has received approximately the same percent of available funds, 6.2 percent, in every year since 1950. Increasing interest in the prostate and in the uterus has been compensated by decreased interest in the kidney, bladder, testes, ovaries, and vagina.

Relative emphasis on studies of the breast has almost doubled from 3.7 percent of 1950 funds to 5.5 percent of 1956 funds.

Emphasis on work on the endocrine system has also increased. In 1950 studies in this field received 3.6 percent of the funds available. In 1956 they received 5.7 percent of a much greater amount. The increased interest in adrenal research, 0.9 to 2.4 percent, and in the pituitary, 0.9 to 2.0 percent, account for most of the change. Research interest in the thyroid, thymus, and parathyroid has fallen off slightly.

Support for work on the respiratory system has increased, from 1.2 percent in 1950 to 2.1 percent in 1956, but hardly in proportion to the attention given this system in other cancer studies outside of the laboratory. This area has been of particular interest to the environmental studies of the Field Investigations and Demonstrations Branch and is the subject of a special program by the American Cancer Society.

Clearly the increase in the extramural research effort during the past three years has been due primarily to developments in the field of chemotherapy, particularly as a result of the stimulation and encouragement provided by the additional funds made available for studies in this area. Not only has this resulted in an increase of 495 percent in support for work in chemotherapy, from $383,000 to 2.3 millions, but also the average size of grants in this field has more than doubled, increasing from $16,650 to $33,550. The increases in the average cost per grant in other methodologic areas have been relatively modest, 15 percent in chemistry and only 6 percent in biology.

Cancer Research Facilities Construction Grants

After World War II, funds were made available in increased amounts in the form of grants and fellowships by a number of agencies to assist experienced investigators to get back into the laboratory and to enable young scientists to continue their training interrupted by the war. With

this emphasis on research and personnel, it became apparent in a few years that space for research was becoming a limiting factor. As a result, the National Cancer Institute became the first of the National Institutes of Health to award grants for the construction of research facilities when the Appropriation Acts of 1948, 1949, and 1950 provided funds for that purpose.

The Acts described the program's mission as follows: "To make grants-in-aid for research and training projects related to cancer including grants for drawing plans, erection of buildings and acquisition of land therefor." From December, 1947 through 1950, the Surgeon General awarded, upon recommendation of the National Advisory Cancer Council, sixty-four grants-in-aid totaling 16.3 millions. Support was awarded to build clinical and laboratory facilities for cancer research at forty-nine non-Federal institutions in twenty-seven states and the District of Columbia. In nearly all instances the grants supplemented local funds.

Although the largest portion of the funds was used to improve laboratory facilities, encouragement was given to the development of a better balance between laboratory and clinical facilities. Grants were made chiefly to medical schools and hospitals closely affiliated with medical schools. In these cases, personnel and facilities were available for both clinical and laboratory research, making possible a broad, well-rounded approach to research problems and facilitating the rapid transfer of laboratory discoveries into clinical evaluation and use. Some grants were made to institutions devoted chiefly to cancer research, even though they were not associated with medical schools or hospitals. The only restriction placed on the use of these construction grants was that the facilities constructed must be devoted to cancer research.

Research

It obviously is not feasible to describe here the results of a research grant program covering a period of twenty years and involving thousands of investigators. However, it may be of some interest to summarize briefly the status of cancer research twenty to thirty years ago and, for comparison, to describe representative recent developments to indicate changes in emphases and viewpoints.

The status of cancer research during the decade prior to the establishment of the National Cancer Institute may be indicated by the following points that are statements of fact or represent viewpoints which seemed to be rather generally accepted at the time. This subject is discussed at greater length in a report, *Fundamental Cancer Research*, by a committee appointed by the Surgeon General in 1937, page 317.

a) A virus had been discovered that apparently induced tumors in domestic rabbits.
b) Mammalian cancer could be transmitted only by grafts of living tumor cells.
c) The first pure chemical carcinogens had recently become available.

d) One of the great needs was recognized as the clarification of the mechanism of action of carcinogenic agents.
e) Evidence indicated that the mode of inherited susceptibility was not the same for all types of tumors.
f) Attempts to establish fundamental differences between normal and malignant cells of the same tissue type had failed to bring out any striking variation in chemical composition, enzyme content, metabolism, or structure.
g) Because of the recognized limitations of cancer therapy, and in order to avoid the many pitfalls, it was felt that a conservative and critical attitude was particularly essential in work in that field.

Carcinogenesis

During the past twenty years a great deal of progress has been made in clarifying the relation of viruses and virus-like agents to the development of cancer in animals. For example, there is now little question that such agents play an important role in the etiology of certain skin tumors in rabbits, mammary and salivary-gland tumors, and, probably, leukemia in mice, kidney tumors in frogs, and leukemia and related diseases in chickens. However, much work still remains to be done to clarify the way in which these agents produce the effects that have been observed.

Perhaps these problems can best be illustrated with the mammary-tumor milk agent in mice, which is transmitted to the young through the milk of the mother. It was found that in addition to the presence of the milk agent, the mice had to be of a certain strain to develop breast cancer. They had to have an inherited susceptibility, a particular genetic constitution, which made them susceptible before the milk agent would induce cancer.

Even in the presence of the proper inherited susceptibility, the milk agent will not induce a high incidence of breast cancer unless the mice are mated and go through the process of pregnancy and lactation with the consequent production of increased amounts of estrogen, progesterone, and prolactin. The need for this hormonal stimulation was confirmed by the injection of estrogen into susceptible virgin mice containing the milk agent. Thus it was clear that the hormonal stimulation of pregnancy and lactation was an essential factor in the induction of cancer by the milk agent.

In the course of extensive breeding experiments, a strain of mice was produced in which there was a high incidence of breast cancer in virgin females that contained the milk agent but had not been exposed to the hormonal stimulation of pregnancy and lactation. These results indicated the presence of some factor that was inherited. Because it apparently served in place of the hormonal stimulation of pregnancy and lactation, it also probably was hormonal in nature. Therefore, it was designated as the inherited hormonal influence.

Further investigations demonstrated that this inherited hormonal influence could be transmitted by at least four strains of mice. At least one

strain would transmit the inherited hormonal influence to its progeny, though its own susceptibility to breast cancer was very low. The fact that the inherited hormonal influence may be transmitted by animals of low inherited susceptibility indicates that, although both of these factors are inherited, they are separate genetically; that is, the inherited hormonal influence is not in itself the basis for the inherited susceptibility to mammary cancer induced by the milk agent.

Therefore, there now appear to be four factors involved in the induction of breast cancer in mice: the milk agent, an inherited susceptibility, hormonal stimulation, and inherited hormonal influence. This illustrates the complexity of what at first appeared to be a rather simple and straightforward problem. If factors of this kind are involved in the induction of tumors by other types of virus-like agents, it would explain why results of various investigations sometimes appear to be in disagreement and why work in this area does not progress more rapidly.

Through the use of ultracentrifugation and electron microscopy, continuing efforts are being made to isolate, concentrate, and visualize the mammary-tumor milk agent. Several investigators have reported the presence of small virus-like particles in cells of mouse mammary tumors that are not found in normal mammary tissues. However, it still remains to be proved that these particles are indeed the active agent or a virus.

One of the outstanding developments in the relation of viruses to cancer during the past several years was the evidence that leukemia and parotid-gland tumors of mice could be transmitted by the injection of cell-free extracts into newborn mice. After a long latent period the injected animals develop a high incidence of one or both types of tumors. The reasons why this procedure is successful only when the extract is injected into very young mice is not clear. Also, it is still to be determined whether both types of tumors are caused by a single agent or whether there are two different agents, though available evidence seems to favor the latter possibility. In other investigations with a different strain of mice, it was possible to transmit in this way what appeared to be leukemia to adult mice in which the disease developed with a much shorter latent period. Investigations have been reported recently in which the activity of the parotid-gland tumor agent of mice has been increased to such an extent that it will induce parotid tumors in six weeks when injected into newborn animals. This increased activity was produced by culturing the agent in monkey-kidney tissue cultures.

During the past twenty years limited progress has been made toward solving the most important problem of chemical carcinogenesis; that is, the mechanisms by which chemicals induce cancer. One important investigation in this field was concerned with the action of the azo dye, *N,N*-dimethyl-*p*-phenylazoaniline, which induces liver tumors when administered orally to rats. It was found that this dye induced cancer only in the liver and only in certain strains of rats. Cancers were not induced in other tissues, other strains of rats, or other animals, like guinea pigs, rabbits, or chickens. In those cases in which cancer was induced, the dye

was chemically bound to certain of the liver proteins. It also was found that the induced liver tumors contained no bound dye and that they seemed to be deficient in some of the protein components characteristic of normal liver.

It was determined that to be strongly carcinogenic the dye should contain at least one *N*-methyl group. A study of the activity of this group during carcinogenesis in both animals and tissue culture revealed that it was converted to a *N*-methylol group before it could be bound to the liver protein. Therefore it was the latter compound that seemed to be the real carcinogen.

From these observations it appears that the formation of the protein-dye complex is a critical part of the carcinogenic action. Because the liver tumors do not bind the dye and seem to lack the protein that binds the dye in normal cells, it is suggested that the actual cause of the tumors is an alteration or loss of specific proteins, which may be essential for the normal control of growth but not for the maintenance of life.

Some further understanding of the mechanism of carcinogenesis has been gained through investigations of the action of ionizing radiations. One investigation has shown that the whole-body X irradiation of mice will produce a pronounced increase in the incidence of lymphatic leukemia. However, the increased incidence of lymphatic leukemia may be prevented if the thymus glands are removed from the irradiated animals. Thus, it might be assumed that the effects of the radiation on the thymus played a primary role in the subsequent development of leukemia. That this is not the total picture is demonstrated by the fact that if unirradiated thymus glands are transplanted into irradiated mice whose thymus glands were removed after irradiation, the increased incidence of leukemia is partially restored. It is apparent, therefore, that the thymus gland is one factor involved in the induction of leukemia. However, the action is not due simply to the effects of the irradiation directly on the gland. The complete explanation of this phenomenon is still to be obtained.

Another investigation has demonstrated that ovarian tumors will occur in all female mice surviving sixteen months after a sublethal exposure (200 r) to X rays at six weeks of age. This effect could be prevented, however, if the exposed mice received transplants of ovaries from unirradiated donors immediately after exposure or up to six months after irradiation. The tumor-preventing action of the transplanted unirradiated ovaries became less and less effective as the interval between irradiation and transplantation increased.

Here again it is doubtful that tumor induction is a direct effect of the irradiation. One possible interpretation of these observations is that during the period of developing maturity after irradiation, the damaged ovaries produce inadequate amounts of estrogen. In an effort to remedy this situation, the pituitary gland produces increasing amounts of gonadotrophins. The irradiated ovary, being unable to respond normally to this increasing stimulation, develops tumors. The implantation of unirradiated ovaries in the irradiated mice restores the reciprocal balance relation-

ship between the ovary and the pituitary and prevents tumor formation. This procedure is effective only if it is carried out before the endocrine imbalance has existed long enough to produce irrevocable cancerous changes in the irradiated ovaries.

Through studies of the action of viruses, chemicals, radiations, and other factors, a great deal has been learned about carcinogenesis. However, as was the case twenty years ago, the fundamental problem of the mechanism of action of carcinogens still remains largely unanswered and represents one of the primary objectives of cancer research for the future.

Tumor Growth and Behavior

Fundamentally, the problem of tumor growth is a problem of tissue synthesis. Knowledge of the development of normal tissues is essential if we are to understand the factors involved in the synthesis of tumor tissue. Therefore tumor growth is concerned with nutrition, metabolism, hormonal influences on tissue synthesis, and nucleoproteins, which presumably control growth and metabolism. Tumor behavior includes the relationship between the tumor and its host, for example, formation of metastases, invasion of normal tissues, and the immunologic reactions of the host to the tumor.

Numerous efforts have been made to determine the growth requirements of tumors in order to see in what way they may differ from those of normal tissues. One approach has been made to this problem through the study of sarcoma 180 growing in tissue cultures. It was discovered that the cancer tissue would not grow in a culture medium containing thirteen essential amino acids, seven essential vitamins, glucose, and appropriate minerals. If this medium was supplemented with 10 percent horse serum, the tissue grew slowly but persistently. However, if 2 percent beef embryo extract also was added to the medium, there was a definite increase in the growth of the cancer tissue.

It is of interest to note that as the cancer tissue grew and was transferred repeatedly to fresh culture media, the rate of growth continued to increase with each successive transfer and finally the presence of the beef embryo extract was not required at all. Nevertheless, when this tissue was transplanted back into the proper strain of mice, it produced sarcoma 180 that was indistinguishable from the sarcoma 180 from which it came. This illustrates how cancer tissue apparently can adapt to various growth conditions and still retain its characteristic neoplastic qualities.

It is widely known that, in both patients and laboratory animals, cancers frequently continue to grow at essentially the characteristic rate even though the host is virtually on a starvation diet; that is, in some way the cancer seems to have first call on the nutritional substances available in the host, even at the expense of the normal tissues. This problem has been investigated by inoculating rats simultaneously with two different rapidly growing cancers, Walker carcinosarcoma 256 and Rutgers I sarcoma. In rats bearing these two fast-growing but dissimilar cancers at the same time, each cancer maintained its characteristic growth rate dur-

ing the early stages of development. In the later stages, however, the growth of the Rutgers sarcoma was reduced and it apparently was unable to compete with the Walker carcinosarcoma, which continued to grow at the usual rate. This indicates that both types of cancer can compete readily against normal tissues for nutritional substances in the body, but as they increased in size and the available food was inadequate to support both of them fully, one type of cancer for some reason was unable to compete with the other. The physiologic basis for this phenomenon is still to be elucidated.

The question of cancer tissues robbing normal tissues of food materials in the blood and tissue fluids also has been studied with the Ehrlich ascites tumor in mice. This kind of tumor is particularly suited for investigations of this type, because the tumor cells are suspended loosely in the surrounding abdominal fluid in which alterations of nutritional components may be readily determined. It was found that the tumor cells rapidly absorbed amino acids from the abdominal fluid. However, the concentration of amino acids in the surrounding fluid decreased only slightly, because apparently they were continually replaced by the release of amino acids from the host tissue. On the other hand, the growth of the tumor cells markedly reduced the concentration of glucose in the abdominal fluid. Presumably the normal tissues are able in some way to protect themselves from the loss of glucose and hence its rapid consumption by the tumor cells was not offset by the transfer of glucose from normal tissues.

A study of the amino acid patterns of a solid type of myeloid leukemia (C1498) growing in two closely related sublines of strain C57BL mice has yielded interesting results. One subline is quite susceptible and the other subline is quite resistant to this type of tumor. In the susceptible subline, the leukemia progressed and killed the mice. In the resistant subline, the leukemia grew for fifteen to twenty days and then regressed. In both types of animals, the amino acid patterns of the leukemia tissue were the same for the first eight days after inoculation. Then the leukemia tissue in the resistant subline began to show an increase in glutamine and glutamic acid, which usually are found in greater concentrations in normal tissues. Thus, it appeared that some condition in the resistant mice made the leukemia regress and caused it to behave, chemically, more like related normal tissue.

Several investigations have been concerned with the metabolism of glucose by normal and cancer tissues. In one study in which glucose containing two or more radioactive carbon atoms was utilized, it was shown that in normal tissue each of the two end carbons of the glucose molecule appeared in lactic acid in equal amounts. This indicated that essentially all the lactic acid was formed by the symmetrical splitting of the glucose chain. In the analogous tumor tissues, however, a preponderance of one of the terminal carbons of the glucose molecule appeared as CO_2, indicating that the metabolism of glucose in tumor tissue differed in some way from that in normal tissue.

There is general agreement in regard to the importance of nucleic acids to cell physiology and metabolism and to cancer research. They are a principal component of genes and chromosomes, which are intimately concerned with the heritable characteristics of cells and which apparently play a critical role in the determination and control of chemical processes in living cells. Thus, studies on nucleic acids and nucleoproteins not only may give some idea of the mechanism by which a normal cell is converted to a cancer cell but also may provide some insight regarding cell metabolism in general.

Research by grantees and others has demonstrated that the effectiveness of aminopterin and amethopterin in inhibiting leukemia is due to their interference with the manufacture of nucleic acids in the cancer cells. Another cancer palliative compound, 6-mercaptopurine, resembles part of the structure of nucleic acids to the extent that it is incorporated in, and prevents the formation of, a normal molecule. The reason why these compounds appear to have a preferential effect on cancer cells is not entirely clear.

Immunology is an area of growing importance in cancer research. An increasing number of grant-supported investigators are directing their efforts toward the analysis and elucidation of the body's natural defense mechanisms against cancer. A very recent investigation has been particularly successful in inducing normal laboratory animals to produce substances that will destroy cancer cells.

Normal laboratory rats were injected with minced human cancer tissue. Seven days after injection, fresh human cancer tissue was exposed for one hour to blood and tissue samples were taken from the injected rats. These human cancer tissues were then implanted into other rats that had been pretreated with cortisone or X rays. Ordinarily, human cancer implants will grow in such animals. In this case, however, the human cancer implants failed to grow. The cancer cells had been destroyed by the cytotoxic substances produced by the rats into which minced human cancer tissue had been injected. Human cancer tissue exposed to the blood and tissue of nonimmunized rats grew readily in animals pretreated with cortisone or X rays.

These cytotoxic agents were found in the blood, spleen, lymph nodes, and thymus of the injected animals but not in muscle, heart, kidney, or lung. This supports the concept that the body's natural defense mechanisms are associated with lymphoid cells. This study also demonstrated that the cytotoxic substances are more potent and are present for longer periods of time in the lymphatic cells than in the blood. It still is not known whether these substances are identical.

For many years the possibility of developing a vaccine for cancer has been considered as one hope for the future, and this investigation has brought the possibility a step nearer.

Detection, Diagnosis, and Epidemiology

Early detection and accurate diagnosis and localization of tumors is important for adequate therapy. If the presence of a cancer can be

detected before it has invaded nearby tissues and before it has spread to other parts of the body, its eradication by conventional surgery and radiation is more likely.

Better means for determining the actual nature of lesions suspected of being cancer are greatly needed. Improved methods of X-ray diagnosis are helpful but are still inadequate. All of the chemical and cytologic methods thus far developed fall short of the need in accuracy and in ease and speed of performance. It is fairly clear that more adequate methods will have to rest on basic studies of the differences between cancer cells and normal cells.

Current studies of biochemical changes in the blood, body fluids, and tissues produced by cancer cells or by their effect on normal tissues or organs offer promise, but no universal test is in sight. Several groups have found abnormal amounts of normally occurring substances associated with a few types of tumors, but these relatively gross changes often occur after the cancer has metastasized. Others have found some abnormal substances in body fluids of cancer patients, but these are rarely consistent or early enough indicators to be of real aid. Studies of certain enzyme levels in body fluids, such as alkaline phosphatase and lactic-acid dehydrogenase, offer encouragement that these or others will provide more reliable means of detecting, diagnosing, and localizing deep-seated tumors. Blood and urinary levels of various metabolic products of tumors, such as steroids, give some leads for certain types of tumors, but methods of detecting and identifying these materials are still laborious and inadequate. Immunologic reactions have been explored and have, as yet, failed to give consistent and reliable means of detection and diagnosis. Effort along this line is continuing.

Studies supported by National Cancer Institute grants are in progress to secure localization of radioactive materials, specifically, in tumors. This method has had some success for brain tumors and for breast rumors. It is still actively under invesitgation in the hope of securing more consistently reliable results. A high-contrast photographic recorder that will scan for tumors made radioactive by chemical means has been developed.

Physical methods like ultrasonic radiation are being developed and tested in two or three laboratories. A somascope has been designed and constructed that converts ultra sound pulses and their reflections into visual images. This gives some promise, particularly, for the diagnosis of tumors of the breast and liver.

Thus far, however, the most reliable methods for diagnosis rely on the trained eye and the microscope. Cytologic methods depend on picking up cells sloughed off or scraped from a tumor. Adaptations of this method for detecting cells shed from the cervix of the uterus have been developed for detecting tumors of the stomach, lungs and bronchial tree, bladder, colon, and other organs. A recent investigation indicated that simply washing out the stomach with saline solution is less traumatic and is more likely to pick up cancer cells for diagnosis than is the use of some special techniques designed for the purpose, such as a rough-surfaced

balloon or a rotating brush. New methods of staining suspected types of cells are being developed and exploited in the expectation that significant differences between normal and cancer cells will be revealed.

Surveys of populations for information on the frequency of occurrence of cancer as a whole or of certain sites may have two major objectives. One of these may be case-finding to determine the magnitude of the situation. This type of study is appropriately supported by funds administered by the Field Investigations and Demonstrations Branch, described elsewhere in this issue.

Another objective may be to discover clues as to etiologic agents that may be contributing to the initiation of certain types of cancer. Such surveys, which reveal certain racial, genetic, cultural, dietary, viral, chemical, or other environmental factors as potential participants in causing cancer, may lead to laboratory or field research to establish the relations or to measures directed toward elimination of the agents and to the prevention of cancer. These studies add to our knowledge of factors influencing the initiation of cancer and means for prevention. They are primarily research approaches and knowledge gained anywhere in the world may provide information that can be applied to the control of cancer in the United States.

Thus, the observation of the high frequency of oral cancer among certain groups in India with peculiar habits in the use of Indian tobacco has led to a grant-supported study of the biological activity of chemically separated fractions of Indian tobacco. No clear-cut results have yet become apparent. Although some of the fractions have caused hyperplasia in the skin of test mice, no cancers have been induced.

Comparison of the results of these studies with other studies in the United States, on the relation between tobacco and cancer, may give some leads as to whether differences in the site of associated cancers are related to differences in tobacco, its method of preparation for consumption, or the way it is used.

Again, the reported observations that primary liver cancer in certain areas of Africa is many times more frequent in Negroes than in other races in the same locations indicated either racial or cultural influences in this disease. To explore this problem, it was necessary to establish the frequency rate for all cancers in these localities and the relative frequency of liver cancer. Work in Johannesburg confirmed the clinical impression and provided a sound basis for other correlated studies. Previous work in the United States had shown that race alone could not be the only factor, for quite different rates of liver cancer existed for Negro populations in the United States. A symposium on liver cancer was held in Africa last summer and as a result a comparative pathologic study of liver cancer in Africa and in the United States is now under way. Grants from the National Cancer Institute help support this activity. Through this and other investigations it is hoped to clarify the relationship of liver cancer to liver cirrhosis. From this also may come leads as to the possible role of

diet, infections, and other environmental factors which may be instrumental agents in the development of primary liver cancer whether it occurs in African natives or United States citizens. Such studies are expected to form a basis for experimental exploration of the causative factors and means for prevention.

Treatment

Surgery and radiation still are the only means of curing cancer and these methods are effective only when the cancer is localized. In the case of surgery, improvements have been made in the pre- and postoperative care of the patient. Through the application of new information on blood transfusion, the use of blood substitutes, intravenous feeding, proper nutrition, the administration of specific hormones, the use of antibiotics to control infection, maintenance of salt and fluid balances, and similar factors, it is now possible to put the patient in better condition than ever before in preparation for surgery. Similarly, these same factors make it possible to keep the patient in optimal condition after surgery and hence give him the greatest chance of survival. These aspects are particularly important in the radical types of surgery, which frequently are the only alternatives for cancer patients.

New methods are being devised to use parts of one organ or tissue to replace parts of another that must be removed because of cancer. For example, pieces of the intestine of the patient may be used to construct a new bladder or to replace a cancerous section of the esophagus. New techniques have been developed in the use of plastic tubing to repair and replace tubes in the body, such as the esophagus and the trachea, and in the application to plastic surgery. Questions are being raised, however, about the use of plastics and synthetic resins in this way in view of the recent demonstration that small pieces or sheets of a large number of plastics induced cancer when implanted in the tissues or under the skin of mice or rats. Efforts are being made to construct surgical blocks in the thigh or upper arm to delay, if possible, the spread of a cancer from the leg or lower arm to the rest of the body. The purpose of this procedure is to give the surgeon time, days or weeks, to find out whether the cancer already has spread to the rest of the body and still not endanger the patient by permitting the cancer to spread during this period. If the cancer already is disseminated, there is no point in removing the limb in an effort to save the patient. These examples illustrate only a few of the many ways in which surgery, generally, and surgery for cancer, particularly, are being improved and developed.

In the case of radiations, the conventional X rays or the use of radium or its substitutes, such as radioactive cesium or cobalt, are still the treatment of choice in general. If the cancer is localized and accessible, cures can be effected. Even if the cancer is generalized or disseminated, very beneficial palliative effects may be obtained in some cases. In view of the importance of these conventional methods, it is not surprising that considerable research is going on to devise new ways to apply and calibrate them and to study their effects. Fine needles or nylon tubes con-

taining radium or its substitutes may be inserted around, or threaded through, a cancer and may then be removed after the proper exposure is obtained. Rotational therapy has been developed in which the patient or the radiation source rotates in such a way that the X rays are continually focused on a cancer within the body. Because of the rotation, the skin and superficial tissues receive much less radiation than the cancer tissue on which the X-ray beam is focused. In this way larger amounts of radiation can be applied to the cancer without causing the serious burns of the skin and underlying tissues that otherwise would result.

Perhaps the most striking recent application of radiations to cancer therapy has been the use of high-voltage or high-energy radiations. Basically this procedure consists of accelerating atomic components, such as electrons, to inconceivably high speeds by the proper application of extremely high voltages. When a beam of these accelerated electrons is directed against an appropriate metallic target, high-energy X rays are produced. During the past several years a billion-volt linear accelerator of this type has been constructed which is 220 feet in length. More recently, however, a midget model has been constructed for clinical and biological applications. It consists of a six-foot long high-vacuum copper tube down which passes a six-million volt electron beam. When this beam smashes against a gold disk, it is converted into a high-energy X-ray beam with an intensity of 100 r per minute. The X-ray beam can be focused to a pin point or it can be spread over an area of 400 square inches. Eighty percent of its output can penetrate to the body's deepest points. Yet these rays are less damaging to the intervening tissues than are the ordinary, softer X rays. There seems little doubt that this type of instrument will play an important role in the treatment of certain kinds of localized inaccessible cancer.

Supervoltage instruments, such as the linear accelerator, betatron, and electrostatic generator, can be adapted to the direct use of the electron beam for therapy. The electrons or β particles are more easily captured by tissue than X rays or the γ rays from radium so that it may be easier to control the localization of their damaging action.

Before leaving this subject, the problem of radiation resistance should be mentioned. Efforts are under way to elucidate the cause and the solution to this critical problem. If a cancer cell or tissue could be induced to take up and retain some compound or chemical, of which there are many, that absorbs a great amount of X rays, the cancer could be made highly sensitive to radiations. Progress in this area is dependent upon a fuller knowledge of the normal physiology of the cell.

The converse step is also an important problem, namely, discovery of chemicals or substances that can protect cells from radiation damage. It has already been shown that unirradiated cells of the spleen or bone marrow inoculated into animals after irradiation, which would otherwise kill all the animals, will preserve life and protect these animals from most of the untoward effects of radiation. Search for the active materials and the mechanism by which they work is in progress. These studies have

important public health, industrial health, and military significance, as we move further into the atomic age.

Research on cancer chemotherapy may be divided into several specific steps, which each candidate therapeutic compound goes through. These steps are to find or synthesize a compound with growth-inhibiting activity, to test the effect of the compound on animal tumors and perhaps on human tumors growing in animals or in tissue culture, to determine its pharmacology and toxicity in animals so the safe and maximal doses can be predicted, to test the compound cautiously in a few patients, and, if still promising, to apply it to as many types of human cancer as possible.

The first step is to find or synthesize compounds that will destroy cancer in man. This may be considered the crux of the whole problem. If we had some way of knowing which compounds to synthesize and if we could devise screening tests to tell us which compounds would be active in man, the problem would be greatly simplified. The choice of compounds to be synthesized has been made on the basis that a theoretical compound should interfere with some specific activity in the cell or that derivatives of a moderately active compound might be synthesized which would be much more active. Developments in this latter area have had some discouraging aspects. For example, there are several compounds (urethan, nitrogen mustard, and 6-mercaptopurine) that have shown profound and prolonged palliative effects on specific types of cancer. Many derivatives of these compounds have been synthesized in the hope that some of them might be more effective and less toxic than the original one. In general, however, this has not turned out to be the case.

The other basis for choosing compounds to synthesize depends upon an intimate knowledge of the chemical machinery of the cell. The basic principle of this approach is to prepare a compound sufficiently similar to some normal component of the cell so that it will be incorporated into the chemical machinery of the cell, yet sufficiently different so that it will block the machinery and sufficiently stable so that the cell cannot convert it into some harmless compound. Finally, the compound should act on cancer cells but not on normal cells. These are stringent requirements to meet. Nevertheless, compounds that fulfill most of these requirements are now available such as the antifolics, which are analogues for and prevent the cells from utilizing the important vitamin, folic acid. Since progress in this area depends so much on knowledge of the complex chemistry of the cell and on chemical differences between normal and cancer cells, there obviously is a great deal of work to be done. On the other hand, in no other area has more progress been made. A number of developments in this area have been described earlier in this report. A great deal of important work is going on and almost every week a new enzyme or a new chemical involved in normal or cancer-cell growth is reported. As a result of additional funds available this year for cancer chemotherapy, hundreds of new compounds are being synthesized and for each one there is some reason to believe it may interfere with cell growth.

It is most unfortunate that there is no preliminary screening method to tell us whether a compound will be effective on human cancer. Of course it is unethical to use new and untried compounds directly on patients. The only alternative is to test such compounds on animals or in tissue culture. We know, however, that animal cancers are not the same as human cancers and that even human cancer tissues growing in animals or in tissue culture are not the same as when they are growing in man.

Despite these difficulties, there has been a marked increase in the screening of compounds. In addition to the synthesized compounds mentioned above, a large number of crude products of bacteria and other microbiological organisms (so-called antibiotic brews), other natural products, such as hormones, viruses, and many other types of material with therapeutic possibilities, are being screened against at least several different types of tumors in animals. Much of the increased activity in synthesis and screening is being supported through the Cancer Chemotherapy National Service Center, which is discussed elsewhere in this issue.

An appreciable number of compounds has been found to inhibit tumor growth in animals. The compound 4-(*p*-dimethylaminostyryl)quinoline and closely related derivatives caused lymphomas to disappear within five to twelve days in all of three hundred rats treated. Similarly treated adenocarcinomas regressed in eighteen to thirty days but sarcomas continued to grow despite treatment. Also, 4-aminopyrazolo(3,4-*d*)pyrimidine selectively damages cancer cells in tissue culture. This compound was effective against HeLa cells, a strain of cells originating from an epidermoid carcinoma of the cervix in a patient. It also was effective against cells of the B-3 mouse carcinoma. Cell division was markedly reduced in the tumor tissues but not in homologous normal tissue.

For the most part, information about the pharmacology and toxicity of a compound is obtained through the use of conventional methods, although sometimes a new type of compound requires the development of new techniques. This work is directed toward the practical problem of determining the lethal or killing dose, the maximum-tolerated dose, and the most effective dose. Frequently the most effective dose is the same as the maximum-tolerated dose and there is very little difference between the latter and the lethal dose. Therefore, these studies must be done very carefully in animals before the compound can be tried, even with great caution, in man.

As is frequently true in scientific investigation, the by-product of this work often is more important than the stated objective. In the process of determining dosage and pharmacology of a compound, a complete study is made of what happens to the compound in the animal and what effects it has. How is it changed chemically? Does it effect specific tissues? How is it excreted? Is it selectively concentrated in any tissue? Answers to these questions are of the utmost importance because they contribute information on how the cell machinery is affected and may

offer leads to the development of related compounds with a highly specific effect and may open up completely new approaches to the whole problem.

Already the list of compounds that have some place in the treatment of one or another type of disseminated cancer is a long one and includes estrogens, androgens, and corticoids; the alkylating agents, such as nitrogen mustards, and phosphoramides; antifolic compounds and other antimetabolites; and the radioactive isotopes of phosphorus and iodine. Each of these compounds has produced useful palliative effects or prolonged remissions against some type of cancer. Ultimately, however, the cancer becomes resistant. Nevertheless, the use of these compounds in patients and animals has contributed information about the way they work and suggestions for the synthesis of related compounds that may be more effective.

In the meantime, additional results continually appear. Dramatic palliative results with Myleran® have been reported in twenty-four patients with chronic granulocytic leukemia. With the same compound, another laboratory has produced remissions for up to forty-eight months in seventeen out of twenty-one leukemic patients.

Chlorambucil has been found to be beneficial in the treatment of chronic lymphatic leukemia, for which X rays have been the accepted method of treatment in the past. This compound also has been found to be useful as an adjunct therapeutic measure in patients with malignant lymphoma, chronic lymphocytic leukemia, and mycosis fungoides. In a study on eight patients with chronic lymphocytic leukemia in another laboratory, chlorambucil was found to be effective, well tolerated, and safe for the short periods used. In still another study it seemed to be of some value in forty patients with Hodgkin's disease.

A new development in cancer chemotherapy during the past year is the organization of some half-dozen cooperative chemotherapy groups in various parts of the country, each of which combines the efforts and talents of four to ten investigators, from several institutions, to attack one or another aspect of this problem. From reports of some seventeen chemotherapy clinics presented at the Third National Cancer Congress in Detroit in June, 1956, it became apparent that it was quite impossible to compare the results from one clinic with those from others, because each clinic carried out the studies under different conditions and no one of them could handle enough patients to obtain definitive evaluations of therapeutic effectiveness in a short time. To obviate these difficulties, cooperative chemotherapy groups have been formed. Each group of investigators decides to concentrate its efforts on the same candidate agents in a few selected types of cancer, to follow the same protocol and, insofar as possible, to carry on its studies in exactly the same way. In this manner the results will be comparable and the total number of patients studied by any single group will be large enough so the results can be analyzed statistically.

As in the case of radiation, the development of resistance to chemotherapy is a serious problem. Ultimately all types of human cancer

become resistant to treatment with chemicals even though they may respond very well at first. Attempts are being made to get around this difficulty by using one compound for a while, then another compound, and perhaps still a third. The resistance to one compound does not necessarily carry over to another. Although these steps have prolonged the lives of many patients, there still is no solution to this problem.

Continuing efforts are being made to treat patients with a combination of two or more compounds at the same time. If one thinks of the chemical machinery in the cancer cell as a chain of chemical processes, it appears that a certain compound may weaken one link in this chain. However, the cancer cell can still recover. If two or more compounds were used that acted in different ways and hence weakened two or more different links in the chain, it might be possible to break the chain and destroy the cancer. Although interesting results have been obtained in this way, it is still too early to say whether this approach is to play an important role in chemotherapy.

There is increasing evidence that chemotherapy can serve a useful function with cancer surgery. It has long been known that surgery for cancer may leave free cancer cells in the wound. In the case of fairly well localized cancer, the wound may be washed with much greater concentrations of chemotherapeutic compounds than could safely be injected into the body. Also, some free cancer cells may get into the blood and start new centers of cancer in other tissues. The possibility that this may be prevented by the injection of chemotherapeutic compounds after surgery is under investigation. It is well known that transplanted cancer tissue is particularly susceptible to treatment during the first few days after transplantation and before it becomes established. On the same basis, it may be that these wandering cancer cells also are susceptible to even a comparatively moderate dose of some chemotherapeutic compound. Preliminary trials in this direction give suggestive hope for benefit, but it is much too early to judge whether or not the method will be effective.

In summary, it is apparent that except for localized cancer that can be treated successfully by surgery or X rays, all of the chemotherapeutic efforts are only palliative. However, this in itself has been a great contribution to the comfort and welfare of many patients and their families. Perhaps of greater importance is the fact that a huge fund of information and a number of promising leads have been obtained on the basis of which we now have some ideas in which directions to go.

After the National Cancer Institute Act was passed by Congress in 1937, the Surgeon General appointed a committee of leading scientists to formulate, as far as this could be done, the fundamental aspects of the cancer problem and to suggest various lines of work which merited investigation. The last sentence of the report of this committee reads as follows: "In any program for cancer research, patience and the adoption of a long-time point of view are absolutely essential." This certainly is still true today. However, there is reason to believe that the point of view need not be nearly as "long-time" as it was then.

Activities of the Field Investigations and Demonstrations Branch

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THIS Branch of the Institute began its operations as the Cancer Control Branch in July, 1947. The programs were directed along two major approaches: (1) extending the application and utilization of current knowledge about human cancer and (2) searching for new knowledge that might be applicable to the cancer problem in humans. From 1947 to 1952 major emphasis was placed on programs directed toward the first approach. In 1953, major emphasis was shifted to the second approach—the acquisition of new knowledge—and the Branch was more appropriately designated the Field Investigations and Demonstrations Branch. The current organization includes the Office of the Chief, Grants Section, Cytology Section, Epidemiology Section, General Field Studies Section, Nursing Section, and Environmental Field Studies Section.

The scope and character of the cancer activities of this Branch have been determined by the provisions of the National Cancer Institute Act of August 5, 1937, as incorporated in the Public Health Service Act of 1944; by recommendations of the National Advisory Cancer Council and its subcommittees; and by the training, experience, and ideas of the staff members who have utilized the team approach to the problems presented.

Cooperation with State Health Agencies

It was the concept of the framers of the National Cancer Institute Act that the goal of better control of cancer in man could be more effectively pursued through cooperation with state health agencies. Soon after the passage of the National Cancer Institute Act, a unit concerned with the development of this idea was established, and the resultant cooperative program is one of the oldest activities of the Institute. A number of states availed themselves of the information services and technical assistance of the unit.

From 1937 to 1942 a small number of Institute staff members was directly concerned with the program. During that period, a number of state cancer programs advanced to a stage where a new specialty in administrative medicine emerged in the form of directorships of divisions of cancer control.

In this same interval a number of projects relevant to state programs

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were conducted. These projects dealt with cancer statistics, incidence, and treatment, such as the pioneer study of cancer incidence—a ten-city morbidity survey conducted during 1937–39; a study of the incidence of cancer of the skin in certain localities in the South as compared with that in certain localities in the North; the preparation of model cancer legislation to be utilized by state health agencies in establishing state cancer programs; and, another activity of note, the appointment of a subcommittee of the Council for cancer nomenclature and records.

With the onset of World War II, the medical staff was gradually drawn off to war-connected assignments, and over-all activity was maintained on a standby basis until late in 1944.

On November 18, 1944, in anticipation of intensified efforts in the cancer field after the war, the Council appointed a subcommittee to study and report on a number of cancer activities, one of which was state cancer programs. The report, published in the April, 1946, issue of the *Journal of the National Cancer Institute* (vol. 6, no. 5), formed the basis for an extensive state cancer control program subsequently conducted by the Institute.

In August, 1946, funds to implement this program—2.5 millions in grant-in-aid funds within the appropriation of the Division of States Relations of the Public Health Service—were made available for the first time to state health agencies for work in cancer control, and a Cancer Control Section was established within the Division. In July, 1947, the Section was transferred to the National Cancer Institute and established as the Cancer Control Branch (subsequently the Field Investigations and Demonstrations Branch). Throughout the subsequent years, the Branch continued to work closely with the States Relations Division, now the Bureau of State Services. In fact, the accounting, bookkeeping, and fiscal audits for the state-aid programs have been performed by the Bureau of State Services for the duration of these programs.

The grant funds were allocated to states on the basis of the following formula: extent of the cancer problem within the state, 35 percent; financial need of the state, 30 percent; population within the state, 30 percent; population density of the state, 5 percent. In the first year of the program, matching of these funds was not required, but in succeeding years, each state recipient was required to match the funds with one dollar for each two dollars of Federal grants. This procedure for fund allotments has continued to the present time.

The state-aid funds could be utilized by the health agencies for a wide variety of programs, such as support of cancer clinics, nursing services, statistical research, cancer registers, professional education, public information programs, diagnostic hospitalization, tissue diagnostic services, training of public health workers in cancer, and administrative costs involved in directing state cancer programs.

To assist states in carrying out their programs, a Grants and States Relations Section and a Public Health Nursing Section were established within the Cancer Control Branch in 1947. The activities of the Nursing

Section in connection with the state-aid program are covered in another section of this report.

To implement medical consultation and assistance to states, an intensive program was undertaken by the States Relations Division in 1946–47. Sixteen medical officers were given orientation in clinical cancer and cancer control. The majority of these physicians were assigned to district offices of the Public Health Service to provide technical assistance directly to state health agencies interested in cancer control. A few were assigned within health departments to assist directly in the conduct of state cancer control programs.

In 1947–48 a clearer definition of the cancer problem was undertaken through a repetition of the ten-city morbidity survey. In addition, a formulation of guidelines for state programs was prepared and distributed through a publication titled *Suggested Activities for State Cancer Control Programs*. These guidelines were further strengthened by the preparation and publication of a cancer manual for Public Health officers, in 1952. The publication of a *Cancer Newsletter* was begun in 1948. Numerous articles for journals, exhibits, and special educational materials for public health workers have been prepared throughout the years.

The pattern of consultation to states, through cancer control consultants assigned to district offices, continued until there was a reorganization into regional offices. At that time, cancer control consultation service was assumed by the central office of the Branch, and this service has been provided to states through the regional offices up to the present.

Almost simultaneously with the reorganization of regional offices and elimination of special program consultants, the program-review procedure for state-aid programs was abolished. This led to the development of an activity-report form that was put into use in 1953 and provides information on state cancer control activities for the Institute.

One of the specific objectives of the state-aid program in cancer was to encourage and assist in the establishment of full-time cancer control programs with full-time cancer control directors in the official health agencies. During the years 1945 to 1950, the official cancer control programs increased from eighteen to fifty-two (forty-eight states and four territories). In this same period, the number of full-time cancer control directors increased to thirty-six. Since then this number has gradually decreased so that today there are only a few giving full attention to cancer control activities. A partial explanation for this situation lies in the fact that recruitment of physicians and other personnel has become increasingly difficult in recent years, and other disease-control programs have emerged, which has necessitated the assignment of additional program duties to those of the cancer control directors. In addition, funds available for this program have fluctuated over the years from 2.5 millions in 1946, to a peak of 3.5 millions in 1950 and 1951, to 2¼ millions in recent years.

In recent years the efforts of the Branch in this program area have been directed toward encouraging official health agencies to combine

their efforts in the cancer field with those of both lay and professional groups in a broad approach to the solution of the cancer problem.

Nursing Activities

While the nursing activities were initially oriented primarily toward programs in cooperation with state health agencies, they have cut across many program areas of the Branch. Subsequently, as the program expanded, the activities became oriented toward the field of nursing research.

In 1947 a public health nursing consultant became the administrator of the Nursing Section. The objectives of the nursing program were outlined as follows:

(1) To prepare nurses to help combat cancer by extending knowledge of the disease to all nurses.

(2) To stimulate better case-finding methods.

(3) To assist in reducing the time between the onset of symptoms and reporting for medical treatment.

(4) To help states to develop an adequate follow-up system on cancer patients.

(5) To improve nursing care for cancer patients.

Speed in implementing the program was essential, since the grants-in-aid cancer money had already been allocated to the states. Therefore, the state directors of public health nursing were in need of assistance in developing the nursing aspects of state cancer programs. To meet this need, an orientation program was planned for all regional and specialized public health nursing consultants of the Public Health Service.

After two work conferences of a month's duration, the regional nursing consultants were able to provide assistance to the state directors of public health nursing. In addition, they formed a reservoir of personnel who could subsequently conduct institutes on cancer nursing throughout the country.

Since achievement of the objectives was dependent upon recruiting a well-informed central nursing staff, attention was focused on acquiring personnel prepared to act as consultants to both public health nursing groups and faculty in schools of nursing. Because visual aids were badly needed, two newly recruited members were assigned, during their orientation program in 1947–48, to assist in the preparation of several sets of slides demonstrating nursing procedures.

In 1948 one nurse was assigned to the State of Washington as a cancer nursing consultant; another was detailed to Maryland where both an extensive state-wide in-service educational program and a bedside nursing program were to be instituted in one county.

It was decided that content material in cancer was the primary need for nurses in teaching and consultation service throughout the country. Consequently, by the end of 1948–49, several university courses and/or institutes had been conducted for public health nursing consultants,

university instructors, and faculties in schools of nursing. One intensive course, supported by a Federal grant, involved the teaching personnel from thirty universities and schools of nursing.

To improve further education in cancer, in 1949 and 1950, central office personnel were loaned to several educational institutions (Yale School of Public Health, Minnesota School of Public Health, and Teachers College, Columbia University).

By 1949 the central office staff had branched into the field of studies and research. An exploratory study on the feasibility of integrating cancer nursing in the basic curriculum was begun at the University of Pennsylvania School of Nursing; a home care study involved the analysis of the cancer case load of the Philadelphia Visiting Nurse Association; a third study involved the analysis of the cancer case load in four selected counties of Maryland.

Concomitant with many of the above activities, the central office staff worked assiduously on the preparation of educational materials. In addition to the preparation of magazine articles and the presentation of papers at meetings, the preparation of a comprehensive manual on the nursing care of the cancer patient was undertaken. The *Cancer Nursing Manual*, published jointly by the National Cancer Institute and New York State Department of Health, has been reproduced in many different languages. It was revised in 1955.

Other publications included a monograph to help nursing instructors broaden their cancer curriculum (Pub. Health Service Publ. No. 147, 1950). This was a long-range project involving the help of a group of nurse educators, clinical instructors, and public health nursing consultants.

The most recent publication, *Tools for the Evaluation of Cancer Nursing* (Pub. Health Service Publ. No. 528), describes three new teaching tools developed in collaboration with an educational consultant and with the schools of nursing that received Federal grants in 1952 for the integration of cancer nursing into the basic nursing curriculum.

Specific research projects over the years have entailed the preparation of a cancer nursing opinionnaire (an attitudes test) in 1950–51; a determination of the amount and types of nursing care given cancer patients at home, 1951–52 (forty-nine agencies); development of tools of evaluation for nursing instructors, 1953–57; a study of the integration of cancer nursing into the program of each specialized nursing consultant in state departments of health, 1955–57; and in 1955, vaginal cytology studies on female employees at the National Institutes of Health.

Through the years it has been the privilege and responsibility of the Nursing Section to work cooperatively with other disciplines in the Branch itself and with nursing leaders throughout the nation in promoting cancer nursing.

Radium Loans

The radium loan program, which during the Institute's first ten years was handled in the office of the Institute Director, was transferred to the newly established Cancer Control Branch in 1947. Under this program,

an institution applies for an amount of radium in the type of applicator most practical for its particular use. In considering applications for loans of radium, a number of factors are taken into account: the training and experience of the radiologic staff; the equipment and facilities available; the need for radium in the community; and the number of cancer patients treated by the hospital. Every effort is made to distribute the radium geographically throughout the country so that as many sections as possible may have the benefits of its use.

The radium is loaned to approved applicants under a contract that is renewable annually. The recipient provides for insurance covering possible loss of the radium.

The major portion of the Institute's 9½ grams of radium has been kept on loan to hospitals for treatment purposes. About 1½ grams have been used at the cancer clinic established by the Institute in cooperation with the Hospital Division of the Public Health Service at the U. S. Marine Hospital in Baltimore, Maryland, and, as needed, some of the radium has been used for research purposes by the Institute's own staff.

Throughout the years this program has been in operation, measurement and standardization of the radium has been accomplished through a cooperative arrangement with the National Bureau of Standards. From 1938 to the present, thousands of individuals have received the benefit of treatment with radium without cost.

Today, the radium, in various types of applicators, is on loan to hospitals with qualified radiologists in approximately sixty institutions throughout the country, located in twenty-nine states and the District of Columbia.

Information Program

The Institute is authorized to collect and disseminate information concerning all aspects of cancer. Cancer information programs for the general public, however, were extremely limited during the early years of the Institute.

Following the establishment of the Cancer Control Branch in 1947, an intensive program was undertaken to develop and produce public information material. Writers were recruited to work with the staff of the Branch specifically for the purpose of preparing this type of material.

From 1947 to 1957 a wide variety of pamphlets, fact sheets, booklets, exhibits, bulletins, brochures, display cards, speeches, films, abstracts, monographs, radio scripts, news bulletins, visual-aid materials, news releases, television material, magazine articles, and material for professional journals and books have been prepared.

During the entire period, the medical staff of the Branch has worked closely with the information staff in responding to thousands of public inquiries received, by mail and telephone, concerning cancer treatment, facilities, examinations, education, and statistics.

Initially, much of the aforementioned material was prepared solely by the Institute staff, but in time, arrangements were made for joint production with the American Cancer Society. More recently, the

Institute staff has developed educational materials which complement those of the voluntary Society and also plans for utilizing such information.

The information material produced under this program has made significant contributions toward increasing the public understanding of the cancer problem. Among these has been a booklet prepared by the Institute staff on cancer facilities and services throughout the country. These data were reported in three separate publications in 1948, 1950, and 1954.

Also notable among these materials has been the film *Breast Self-Examination*, which was conceived by the Institute staff and prepared and produced in conjunction with the American Cancer Society in 1950. This film has had by far the widest circulation of any film ever produced in the health field.

Another film, *Challenge—Science against Cancer*, was produced in 1950 in cooperation with the Department of National Health & Welfare of Canada. This was directed toward science students in high schools and colleges, as well as the general public.

A book titled *The Challenge of Cancer*, by Lester Grant, dealing with cancer research for the public, was produced for general distribution under Institute sponsorship in 1950

The film, *The Warning Shadow*, directed toward males over forty-five years of age, urging them to seek periodic chest X rays from their physicians, was produced in 1953 in conjunction with the American Cancer Society.

The foregoing are only a few of the noteworthy contributions made by the Branch in this field. In general, the public is better informed about cancer today than at any time in history. The public understanding of the cancer problem in America has markedly increased in recent years, and it is believed that these efforts on the part of the Institute have been, at least in part, responsible for this development.

Clinical Traineeship Program

The framers of the Cancer Institute Act were impressed by the need for cancer training. To implement this training, the Surgeon General appointed a committee of the National Advisory Cancer Council to study the matter. This group recommended that in order to promote the wider use of the best methods of diagnosis and treatment, training opportunities should be provided for physicians who wished to specialize in cancer work. A clinical traineeship program based on their recommendations was begun in the fiscal year 1938.

Under this program a graduate from an approved medical school who has completed a year's approved internship and who is not over 40 years of age, may be eligible for training provided he intends to devote himself to clinical cancer work. The physicians receive a *per diem* stipend while in training. On advice of the Cancer Council, this stipend was initially $6 per working day and was raised in the intervening years to $8 per day,

then to $10, and, at present is $3,800 for the first year, $4,200 for the second, and $4,600 for the third, with an additional annual allowance of $350 for a spouse and each dependent child, plus a travel allowance to the training center. Appointment as a trainee is necessarily contingent upon the acceptability of the applicant to a training center. Also more recently, in addition to an internship, an applicant has been required to have one or more years of residency training in a specialty related to cancer. Trainees are permitted to receive up to three years of support.

This program had been curtailed considerably as a result of lack of eligible candidates during the war. In the report of the National Advisory Cancer Council, previously referred to, the Council had strongly recommended an increase in this activity, and a beginning had been made in 1946–47 when the Institute received its first increase in appropriations. In July, 1947, when the Cancer Control Branch was established, it was given the responsibility for the administration of the clinical traineeship program. Under this guidance the program has increased in size and scope to the point where 161 trainees are currently in training (May 31 figure), and funds available for this purpose amount to $730,000.

In the early years of the program, most of the trainees were placed in large training centers in the Eastern United States. However, over the years, as other centers developed their cancer training facilities, an effort has been made to distribute the traineeships geographically throughout the country so as to extend the number of training centers and reach a larger number of individuals.

Under this program hundreds of graduate physicians have obtained special training in the diagnosis and treatment of cancer. By far the majority of these physicians have continued in the cancer field. Many of these trainees have gone into academic medicine, and as faculty members and cancer coordinators, they are providing cancer training to others through their associations with professional schools and cancer clinics throughout the country.

Cancer Teaching Program in Medical Schools

One of the subjects studied by the Committee on Cancer Services and Facilities appointed by the National Advisory Cancer Council, in November, 1944, was medical education in cancer. On the basis of this study the Council made a recommendation that a conference of deans, medical educators, and others interested in medical education, be called to review the teaching of cancer. This conference was held in November, 1946, and culminated in a report of the National Advisory Cancer Council (*Cancer Teaching in the Medical School Curriculum*) which recommended that the National Cancer Institute undertake a program of financial assistance to medical schools to coordinate and improve the teaching of cancer to undergraduates and that the Institute request appropriations sufficient to enable it to carry out the foregoing recommendation.

In July, 1947, with the establishment of the Cancer Control Branch, the responsibility for developing and directing such a grant program was placed within that Branch. Under this activity each of the approved four-year

medical schools receives a grant up to $25,000 annually, and each two-year medical school receives a grant up to $5,000 a year, for the broad purpose of correlating and improving its cancer instruction. Within this general purpose, the schools have been permitted maximum latitude to develop the type of program that best meets their particular circumstances. Applications for grants to support this activity are reviewed by both the Cancer Control Committee and the National Advisory Cancer Council and awards are made on the basis of their recommendations.

The administration of the program permits maximum flexibility in the use of funds in order to assure the academic freedom that is necessary in professional education. In addition, it has always been felt that direction of teaching programs must not come from the outside but must be intramural and autonomous. This belief has been justified by the widespread acceptance of the program. Over the years all the approved medical schools have come to participate in the program. The program was extended to the six approved four-year schools of osteopathy in 1951.

The need for evaluation of the effects of the program led to the development of a cancer-knowledge test that is given on a voluntary basis to medical students throughout the country by a special unit of the University of California School of Medicine. Similar tests also have been devised for dental and nursing students.

This activity constitutes the first successful venture of the Public Health Service in the field of aid to medical schools for instruction in a specific disease category and has resulted in measurable improvement in cancer education. Current funds available for support of this program are approximately 2.5 million dollars.

Cancer Teaching Program in Dental Schools

This program, which is parallel to that in medical schools, permits grants up to $5,000 annually to be made to dental schools for instruction of undergraduate students in the recognition of oral cancer. The basis for this program, which was initiated in the fall of 1947, is the fact that a large proportion of oral cancer cases is first seen by dentists and only a limited percentage of these are recognized as malignant conditions requiring immediate referral for adequate medical attention. If the undergraduate dental student could be instructed in the recognition of oral lesions, he could be instrumental in the early diagnosis of such cancerous conditions.

The program is operated under the same administrative arrangements and policies as the medical-school-grant activity within the Branch. This program, too, has had widespread acceptance and has been enthusiastically received by practically all approved dental schools. Approximately $210,000 annually is currently utilized for support of the program.

Cancer Teaching Program in Schools of Nursing

In 1952 the Branch undertook a program of grant support to five schools of nursing, geographically distributed in the Northeast, East,

South, Midwest, and Far West, directed toward the improvement and integration of cancer nursing in the basic professional nursing curriculum. The grants were awarded on a pilot basis in the amount of $10,000 annually for five years. The program was intended to determine the most practical methods of providing future graduates with a better understanding of cancer and to equip them to handle cancer nursing activities. Although this program is not completed in all of the schools, patterns of integration have evolved, and further experimentation in curriculum revision is planned.

Cancer Teaching Program in Schools of Public Health

In 1948 the Branch initiated a program of grants to three schools of public health in order to provide instruction for health department personnel in the public health aspects of the cancer problem and to train cancer control administrators. The program continued for a period of six years and met with limited success in accomplishing its objectives. Unfortunately, only a few individuals so trained continued in the cancer field in official health agencies. Recently (1956) there has been a renewal of interest by schools of public health in this type of program.

Professional Education

With the organization of the Cancer Control Branch in 1947, an expanded program directed to cancer education for all professional groups was undertaken, and a Professional Education Section was established within the Branch.

Numerous attempts were made to bring recent information about cancer directly to practicing physicians. One of the most important of these has been the development, production, and joint distribution, by the Institute and the American Cancer Society, of a series of films for professional audiences depicting the early diagnosis of cancer. In this series there have been individual color and sound films dealing with the diagnosis of breast, gastrointestinal, uterine, lung, and oral cancer. These films were produced at approximately year-and-a-half intervals and released over a period of years, after 1948. The films have been widely distributed and used.

A series of lantern slides and color transparencies illustrating cases of clinical cancer and a second series presenting cancer statistics were developed for use of the general practitioner and distributed on a loan basis to medical societies and others.

The development of a national publication on cancer diagnosis and treatment for the use of practicing physicians, the *Cancer Bulletin*, and its free distribution to physicians within the states have been encouraged by urging state health agencies to use their cancer control grant-in-aid funds to purchase the publication. At one time this publication had a distribution among physicians second only to the *Journal of the American Medical Association*. The *Bulletin* is still being published, although its circulation has dropped.

Another significant effort in the information program for physicians has been the development, organization, promotion, conduct, and support of three national cancer conferences. In this area, attempts were made to bring together clinicians, research workers, public health workers, and others interested in the cancer problem, so that all groups could be apprised of the latest cancer information in their respective fields of interest and some attempt could be made to coordinate their efforts. Since 1948 such conferences have been held at four-year intervals in major cities under the joint sponsorship of the American Cancer Society and the National Cancer Institute.

Numerous educational and scientific papers and exhibits designed to impress upon the physician and dentist the need for early diagnosis and to teach early recognition of cancer have been prepared for use at professional meetings of all types throughout the country.

Cancer symposia, cancer teaching conferences, refresher courses, and similar undertakings for practitioners have been encouraged, sponsored, and financially supported over the years through various grants provided by the Branch.

Cooperative working arrangements have been developed, maintained, and strengthened with all manner of professional organizations throughout the country in order to bring about the appropriate dissemination of cancer information and to promote the coordination of cancer activities.

Field Investigation Grants

In the fall of 1947 a program was established under which grants could be made, on a project basis, directly to universities, medical centers, institutions, laboratories, professional societies, and voluntary organizations interested in the control of cancer. This program was for the following purposes: to bridge the gap between basic or fundamental cancer research conducted in laboratories, which was the type largely supported both within and without the Institute prior to 1947, and research on the cancer problem in human populations; to utilize the skills and disciplines of scientists, clinicians, and clinical research workers and to bring them closer together; and, finally, to provide a mechanism through which research findings could be applied to the human problem.

The initial appropriation for this activity, which was established as the Special Project program, was approximately one million dollars. This appropriation has continued at about the same level until 1956 when it was raised to 1.3 million.

In the initial operation of the program the National Advisory Cancer Council undertook to review and make recommendations on all requests for grants. However, as the program developed, it became apparent that additional assistance was needed in reviewing these applications, and a Cancer Control Committee was established to review the project requests in detail and make recommendations to the Council. This Committee was organized in March, 1948, and its membership was composed of individuals who were interested in cancer but were not in government

service—in the fields of surgery, radiology, pathology, internal medicine, preventive medicine, medical school administration, state health department administration, and state cancer control administration. The Committee has continued to assist the Council by functioning as a preliminary reviewing body throughout the years.

The Special Project program, later renamed the Cancer Control Project program, and, more recently, the Field Investigation Grants program, has accomplished to a considerable extent all its original objectives.

Numerous significant studies have been supported in a wide variety of fields, including applied and developmental research, with noteworthy contributions resulting from a high percentage of the investigations. This program was the forerunner of some of the more recent grant programs of the Institute and has been a prototype for programs in other institutes interested in this field of research.

Epidemiologic Studies

In the early years of the Cancer Institute, only a limited amount of funds was available for the development of the epidemiologic approach to the cancer problem. To expand work in this area, the Cancer Control Branch established the Epidemiology Section on June 1, 1948. Initially, the staff of this Section reviewed data that had been collected in a small number of previously conducted epidemiologic surveys in order to determine whether such data could be made more useful through study and analysis. Throughout the years, data have been assembled on many special problems related to the occurrence of cancer in humans. Many special epidemiologic studies have been initiated in recent years with the cooperation of medical centers, hospitals, and professional groups. In addition, field investigators have been assigned to schools of medicine and public health to develop epidemiologic studies. A special unit for the study of the epidemiology of lung cancer is operated by the Branch in conjunction with the University of Pittsburgh. Data are accumulating in this field, and some significant facts about the etiology of cancer are being revealed by the analysis of selected portions of this material.

Environmental Cancer Studies

Increasing attention has been given to environmental factors that may have a relationship to cancer. With the establishment of the Cancer Control Branch, the potentials of environmental cancer studies could be exploited, and an Environmental Cancer Section was established in April, 1948. A number of cooperative occupational cancer studies and surveys, in selected industries in Ohio, Maryland, New Jersey, Pennsylvania, Utah, and Colorado, were undertaken. The activities of this Section were expanded in 1949–50 to include a cancerigenic research laboratory at Georgetown Medical School where animal experiments could be conducted that utilized suspected carcinogens obtained from various industries.

Numerous field studies and investigations have been undertaken directly by this Section or have been supported through grants that have

immediate bearing on environmental factors. Staff members of this Section have been assigned to field units throughout the country to carry out these studies. One of the major studies in this area has been the establishment of a medical-examination program for uranium miners of the Colorado-Utah Plateau. This study was organized in 1953 and has continued in operation up to the present. Another recent major undertaking has been the organization, construction, and staffing of an environmental cancer research laboratory in Hagerstown, Maryland, through which studies will be made of all manner of environmental factors in soil, air, water, and the general environment. Out of these studies has come the recognition that some environmental factors related to cancer may involve many persons in our present-day population.

This is an aspect of the cancer problem that has come under systematic study only recently and in which increased efforts offer unlimited possibilities for making significant contributions to the solution of the cancer problem.

Biometric Studies

A Statistics Section was organized within the Branch in 1947. This Section developed a number of cancer studies of a statistical nature, such as the ten-city morbidity survey in 1948 and 1949, a statewide cancer morbidity survey in Iowa in 1950, and a countywide morbidity survey in Shelby County, Tennessee, in 1951–52. Through technical advice and consultation during these years, a number of states were assisted in developing and conducting more uniform and adequate statistical programs. In 1951 this Section became a separate Branch. Subsequently, its work was oriented toward clinical and laboratory research, with special consideration of therapeutic trial design, evaluation of end results in cancer, and bioassay techniques, as well as a continuation of its work in demography and experimental statistics.

Field Investigations

In 1947 a Technical and Demonstrations Section was established within the Branch to develop methods for early detection of cancer cases and to demonstrate these procedures. It was renamed the Field Studies Section in 1950 and in 1953 became the General Field Studies Section.

One of the significant undertakings of this Section has been the establishment of field research projects in exfoliative cytology. A pilot project in vaginal cytology, established in 1947 in Hot Springs, Arkansas, was moved to the Department of Pathology, University of Tennessee Medical School, in 1951, in order to expand the research activities in vaginal cytology. The program in Memphis included the study of the general female population, in order to obtain epidemiologic data on the efficacy of the cytological method and information on early detection of cancer in a curable stage and prognosis in treated cancer. The studies in Memphis continue in full-scale operation.

Information obtained thus far encouraged the National Cancer Institute to expand the cytology research program, in various medical centers, to

include many new aspects of the application of vaginal cytology. A Cytology Section was established in 1956, and new field research programs are under way in Columbus, Ohio, Madison, Wisconsin, Washington, D. C., Philadelphia, Pennsylvania, Houston, Texas, San Diego, California, and Louisville, Kentucky.

More recent developments in the field of exfoliative cytology have indicated the usefulness of the method in sites other than the vagina. The program now includes research in cytology of sites such as the lung and large bowel.

A three-year cooperative program with the Maryland State Department of Health was initiated to demonstrate the effectiveness of certain cancer control procedures at the local health department level. These techniques included cancer reporting, epidemiologic surveys, evaluation of the availability and utilization of cancer control services at the county level, and evaluation of the contribution of an adequate, generalized public health nursing service to the cancer case-finding program of the community.

A cooperative project, in the Public Health Service dispensary of Washington, D. C., was undertaken to provide cancer services to Public Health Service beneficiaries and to demonstrate the value of integrating cancer detection services into the activities of Public Health Service dispensaries and hospitals. This project also continued for a number of years.

A demonstration was conducted in connection with the Iowa State Health Department that was designed to bring cancer technical services to rural communities.

Another activity was undertaken, in connection with the mass tuberculosis survey performed in Seattle, Washington, to evaluate the effectiveness of the mass X-ray screening technique in uncovering early cases of pulmonary cancer.

In 1948 the compilation of a bibliography was started on cancer diagnostic tests reported in the literature. This compilation required a number of years to complete.

In the summer of 1948 a conference was held in Chicago for the purpose of discussing the evaluation of cancer diagnostic tests and reaching a common agreement as to the methodologies to be used. Later in the year, a clinical-trials unit was established by the Branch at the University of Washington, in Seattle, to evaluate certain so-called diagnostic tests reported in the literature.

A similar conference was held in the fall of 1949, after which the Universities of Kansas, Tennessee, and Alabama, and Tufts Medical College, Boston, were awarded grant support to carry out diagnostic-test evaluations.

In this area, up to the present, the Branch has continued to encourage, support, and conduct diagnostic-test evaluations. The clinical-trials unit was moved from Seattle to Bethesda in 1953 and the field laboratories supported under grants were reduced from five to three,

located at the University of Kansas, the University of Tennessee, and Tufts Medical College. Although no suitable general diagnostic test has been developed to date and a review of numerous tests shows negative results, interest in this field is continuing.

The demonstrations initiated by the Section were largely brought to a conclusion by 1952 and few new ones have been undertaken since that time. Emphasis has been shifted to other phases of the program. The Section has been enlarged by the addition of several field investigators, primarily medical officers, who have been assigned to medical schools and other centers to carry out clinical epidemiologic investigations that show promise of contributing new knowledge to the occurrence, nature, and course of cancer in human populations. These research studies extend from coast to coast and cover thirty to thirty-five special aspects of cancer.

In the ten years the Branch activities have been in operation, a surprisingly large number of goals have been realized. This has resulted from the combined efforts of many individuals, professional and nonprofessional, representing a variety of medical and scientific skills. There is a continuing need to improve the nature and effectiveness of the over-all program, which will be improved as the investigations under way reveal more knowledge about the carcinogenic process with regard to prevention, diagnosis, and treatment of human cancer.

The Chemotherapy Program

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Background

THE national program of voluntary cooperative research in cancer chemotherapy is the newest and largest special program of the National Cancer Institute—representing nearly half of the total budget. Its inception is indicative of the striking change in attitude toward research in cancer chemotherapy. Previously, disappointments had been so numerous that many investigators doubted that such research could ever succeed. Recognition of the potential usefulness of chemotherapy resulted from a number of developments, among them the successes achieved with the sulfa drugs and the antibiotics and the demonstration that today there are chemical agents capable of temporarily controlling some forms of cancer. For example, such alkylating agents as nitrogen mustard produce full, though temporary, remissions in chronic leukemia, Hodgkin's disease, and other lymphomas. Antimetabolites, such as amethopterin and 6-mercaptopurine, produce spectacular temporary remissions in acute leukemia. Steroid hormones are now standard therapy in several forms of cancer; male hormone produces remission in 20 percent of metastasized breast-cancer cases, while female hormone produces remission in 80 percent of patients with metastatic cancer of the prostate. Cortisone temporarily halts the progress of leukemia. Antibiotics, such as the actinomycins, azaserine, and 6-diazo-oxo-L-norleucine (DON) are extremely active in animal tumors and are under study in man.

The national program was initiated in July, 1953, when Congress requested the National Cancer Institute to explore the feasibility of an engineered, directed extramural research program in the chemotherapy of acute leukemia.

An *ad hoc* committee of experts under the chairmanship of Dr. Walsh McDermott was appointed to make recommendations. There ensued a series of discussions regarding the concept of research directed from the Federal level. The consensus was that a program engineered and directed by the Federal Government would not be appropriate, for psychological as well as technical reasons, and that fundamental research could best be accomplished in the traditional atmosphere of independent research. At the same time, recognizing the need for cooperative studies in certain

Journal of the National Cancer Institute, Vol. 19, No. 2, August 1957
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areas, the committee agreed that the National Cancer Institute could promote that cooperation by bringing scattered groups together in meetings and symposia and by improving the exchange of information. Accordingly, in late December, the National Cancer Institute settled upon a program philosophy of voluntary cooperation, and, as the initial step, a series of large research grants amounting to almost one million dollars were made to a few research institutes and medical schools for the purpose of establishing or expanding integrated cancer chemotherapy research programs.

Congressional interest continued to increase and by July, 1954, it was decided that some form of interinstitutional cooperation would be necessary. To lay the groundwork for this cooperation a new advisory committee—the Cancer Chemotherapy Committee of the National Advisory Cancer Council—was established under the chairmanship of Dr. Sidney Farber. Several devices for improving communication were evolved: *a*) publication of *Current Research in Cancer Chemotherapy*—a newsletter for informal exchange of information, *b*) initiation of a series of regional, national, and international seminars and symposia, and *c*) compilation of an annotated bibliography of the world literature on cancer chemotherapy. At this time, the American Cancer Society and the Damon Runyon Memorial Fund for Cancer Research joined the National Cancer Institute as cosponsors of the program and named representatives to the Cancer Chemotherapy Committee. During the year beginning July 1, 1954, the National Cancer Institute increased its grant support in the chemotherapy area to approximately three million dollars.

Although these initial steps were felt to be of great value, Congress soon envisioned a much larger and more highly integrated program. To this end the National Cancer Institute undertook the following: *a*) establishment of a staff to operate the program, *b*) enlargement of the group of sponsors to include the Atomic Energy Commission, the Veterans Administration, and the Food and Drug Administration, *c*) establishment of appropriate advisory committees, and *d*) creation of a contract program for the support of research and services, initiated at the request of the National Cancer Institute and over which the Institute exercises continuing control.

In April, 1955, the Cancer Chemotherapy National Service Center was established as the staff organization responsible for the program. Since the National Cancer Institute was to provide the major financial support, the Service Center was made a part of the Institute at Bethesda. Its functions are to manage the National Cancer Institute's portion of the program, undertake direct responsibility for contractual research, appoint needed technical advisory panels, arrange for exchange of information, promote voluntary cooperation among scientists, and render technical and other services to cooperating scientists.

The other sponsoring agencies also contribute varied and valuable support to this cooperative effort. The Damon Runyon Memorial Fund supports research and training. The American Cancer Society supports

research and training as well as lay and professional education in matters pertaining to cancer. Pharmacological and toxicological tests on promising drugs are carried out by the Food and Drug Administration. Facilities for the synthesis and evaluation of radioactive chemicals are provided by the Atomic Energy Commission. The Veterans Administration has hospitals where clinical studies of anticancer agents are conducted. Since the daily census of malignant-disease cases is between 3,000 and 4,000 in these hospitals, large-scale statistically significant evaluation of agents can be carried out with long-term follow-up.

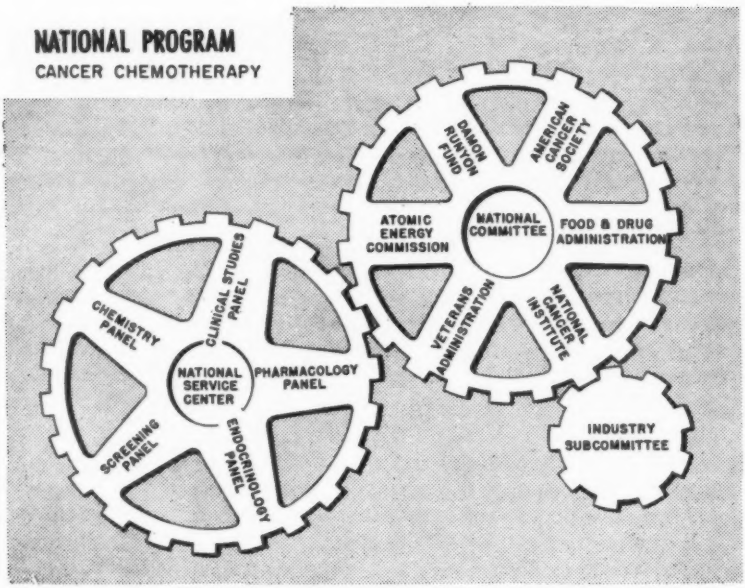
Because of the importance of coordinated effort among the sponsoring agencies, a top policy-making committee—the Cancer Chemotherapy National Committee—was created in June, 1955. Under its charter, the National Committee consists of a representative of each sponsor, plus a member from industry and a member at large. The chairman is *ex officio* chairman of the Cancer Chemotherapy Committee of the National Advisory Cancer Council and the Secretary is *ex officio* Chief of the Cancer Chemotherapy National Service Center. The sponsors are not bound by decisions of the National Committee and each sponsor retains control of its own funds.

Recognizing the vital role of industry in a drug-development program of this nature, the National Committee promptly established an Industry Subcommittee to give advice on the promotion of industrial participation. This Subcommittee is composed of industrial research executives, serving as private individuals and not as company representatives, who are informed as to industry facilities, interests, and problems.

Four advisory panels, Chemistry, Screening, Pharmacology-Biochemistry, and Clinical Studies, were appointed in June, 1955, to give the program direction. A fifth, the Endocrinology Panel, was added in June, 1956. These technical panels assess the state of knowledge in their particular field to find promising avenues of approach and advise on technical aspects of the national program.

The relationship of these groups can be seen in text-figure 1.

In the year beginning July, 1955, the congressional appropriation was increased to five million dollars. The contract program was launched and the first major interinstitutional projects were started. Upon the advice of the Screening Panel the first major contracts were let for four screening centers, which operate through the Service Center and accept chemicals and natural products submitted by interested investigators for tests against animal tumors. A policy for limited confidential handling of data was adopted in order to protect the rights of suppliers. The Chemistry Panel established a program of supplying chemicals to cooperating investigators for use in all phases of cancer chemotherapy research. A pharmacology service laboratory was set up in the Food and Drug Administration to perform toxicological and pharmacological studies on carcinolytic agents. Under the guidance of the Clinical Studies Panel, a number of cooperative clinical study groups were established in approximately forty hospitals.



TEXT-FIGURE 1.

July, 1956, brought a fourfold increase in appropriations, to the level of 19 million dollars—a sum greater than the total appropriation of the National Cancer Institute three years before. Of this, Congress earmarked five millions for research on steroid hormones. The Endocrinology Panel was formed, and, under its guidance, hormone assay laboratories and clinical testing groups were launched. The screening program expanded rapidly, necessitating a program for inbred-mouse production since demands for such mice rose to the level of two million per year, more than the prevailing supply. Perhaps the most significant development of all was the fact that most of the pharmaceutical companies became actively interested in the program, submitted materials for screening, and began to develop cancer chemotherapy programs of their own.

The Empirical Program

In the present state of knowledge, the search for chemical cures must proceed to a large extent on an empirical basis. The random screening of large numbers of chemicals and natural products turns up "leads," and their exploration results in the synthesis and testing of related materials. From such empirical research there gradually emerges a body of data that makes generalizations and rational approaches possible.

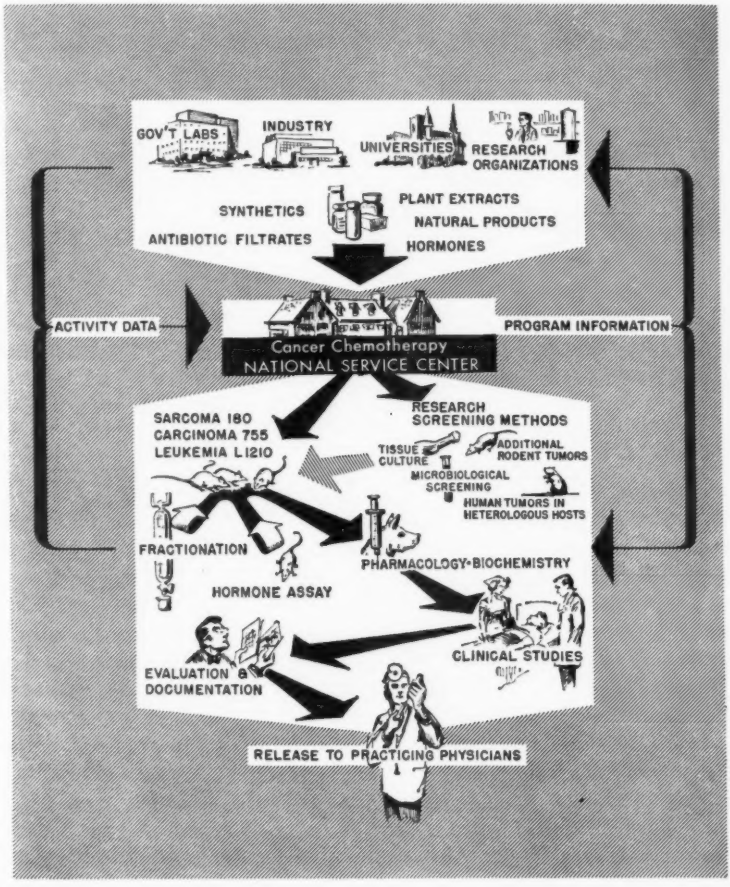
At the same time, biochemical studies of cells and of growth and reproduction, though not directed toward chemotherapy, yield information that permits the chemotherapist to experiment on the basis of testing rational hypotheses.

The existing program is a mixture of empiricism, exploration of existing leads, and active support of that basic research which appears to offer the possibility of yielding useful information. The functional steps into which such a program can be divided are schematically shown in text-figure 2.

Screening

The heart of any empirical drug-development program is screening. Today there are modest screening programs in several pharmaceutical houses and a few universities; the two largest programs are those of Chester Stock at the Sloan-Kettering Institute and the contract laboratories of the Cancer Chemotherapy National Service Center.

At present, each year under the program of the Service Center, some 45,000 synthetic chemicals, antibiotic "beers," steroids, and plant extracts



TEXT-FIGURE 2.—Schematic flow chart showing relationship of activities sponsored by the Cancer Chemotherapy National Service Center.

are being tested for antitumor activity. There are two major sources of chemicals: 1) the off-the-shelf selection of chemicals from educational institutions, research organizations, and manufacturing concerns; 2) active programs of synthesis based on existing leads arising from compounds that have shown activity. Such programs of active synthesis have been in operation in several pharmaceutical houses or have been supported in other institutions by grants-in-aid or by contracts.

The compounds are screened in one of six new screening laboratories under contract to the Service Center. The flow of compounds to these contractors is controlled by the Service Center, and the methods used are those recommended by the Screening Panel.

Tumor screens used are the solid subcutaneous forms of sarcoma 180 and adenocarcinoma 755, and the ascitic form of leukemia L1210. Compounds are screened at the maximum-tolerated dose and are considered potentially active when they meet certain minimum standards of activity in three consecutive tests on the same tumor at the same dose. They may be rejected as inactive at any stage. Results are sent to the supplier in about three months.

The screening problem is highly complex. Each type of tumor in animals shows its own range of sensitivities to a series of drugs because of its physiological and biochemical makeup, which discerns different pharmacological properties of the test drug. In addition, the same type of tumor in different species varies in its sensitivity to a particular chemotherapeutic agent. For these reasons, one cannot predict which, if any, human cancer will respond to a chemical that is highly active against a particular animal tumor.

There is no simple solution to the screening dilemma. The difficulties will continue until a system can be defined that bears a direct and consistent relationship to the response of human cancer. In the meantime, screening systems are being improved wherever possible, in part by correlating the activity of a drug in each screening system with its therapeutic activity in each type of tumor in man.

Since there is no single tumor that will select all useful agents, a tumor spectrum is mandatory for an optimal screening operation. The choice of tumors for the program was based on the Gellhorn report [1] and represents a compromise. The mouse tumors—sarcoma 180, adenocarcinoma 755, and leukemia L1210—were chosen because together they are capable of detecting all compounds known to be active, and they have had the lowest combination of false positives.

Sarcoma 180 has nearly 100 percent transplantability, low regression rate, rapid growth, lack of host-strain requirement, and apparent intermediate sensitivity to several adverse agents. It has detected or confirmed the activity of nearly all compounds that are used clinically, with the exception of the steroids. These include the antifolics, urethan, the nitrogen mustards, triethylenemelamine, the phosphoramides (such as TEPA and thio-TEPA), 6-chloropurine, thioguanine, and 6-mercaptopurine. Adeno-

[1] Investigations of diverse systems for cancer chemotherapy screening. Cancer Res. Suppl. No. 3, 1955.

carcinoma 755 is sensitive in picking up antagonists of nucleic acid metabolism. The choice of L1210 as a representative leukemia was made because the greatest amount of information was available on screening with this tumor. It has revealed the effectiveness of the nitrogen mustards, triethylenemelamine, folic acid analogues, and other less active materials.

It is evident that the current methods do not necessarily represent the best tumors and techniques nor the only ones to be used. Other combinations of rodent tumors are being used effectively in several laboratories. Human carcinomas and sarcomas grown by continuous passage in cortisone-treated rats and hamsters and in chick embryos are finding increasing use. There is a growing interest in tissue culture as a primary screening method.

Through the initiative of individual investigators or supplementary stimulus from the Screening Panel, various leads on new tumors or techniques are being studied sufficiently to permit a fair appraisal of their potential usefulness. Some of these are:

1) Investigation of human tumors in tissue culture, in the embryonated egg, and heterologous mammalian hosts (hamster, rat, mouse).

2) Studies to learn whether the ascitic form alone of nonlymphomatous tumors is too sensitive and, if so, whether a test of the proper degree of sensitivity may be devised to utilize this form of cancer.

3) Other, newer tumors, including spontaneous tumors.

4) Tumors in histocompatible hosts.

5) Use of a group of different leukemias, including those in high-leukemia-incidence strains.

6) Combination screening.

7) Investigation of a variety of microbiological test systems, alone and in combination, as possible alternatives for tumor systems.

Another problem in the screening area is that the magnitude of the screening operation has vastly increased the demand for inbred mice and is taxing the facilities of mouse breeders operating within the United States. The Service Center therefore is expanding facilities for production of inbred mice, since two of the three tumor systems used in the screening program—adenocarcinoma 755 and leukemia L1210—require two specific strains of mice. Fortunately, if these two inbred strains are crossed, the first generation will carry both tumors.

In order to secure adequate supplies of mice, the Service Center sought the advice and help of the Institute of Laboratory Animal Resources of the National Research Council. The Institute drew up minimal specifications for genetic control, sanitation, etc., which serve as the criteria for a voluntary program of inspection, accreditation, and certification of mouse breeders. Under this program, genetic centers supply com-

mercial mouse breeders with the two genetically controlled inbred strains. These mice are then cross-bred by the commercial breeder and the first generation offspring are available to screening laboratories.

To circumvent the danger of ectromelia outbreaks, the Service Center has sponsored an ectromelia diagnostic service at the Hahnemann Medical College, Philadelphia, Pennsylvania, under the direction of Dr. Bernard A. Briody. This service is available to both breeders and users of mice.

Preclinical Pharmacology

When a compound shows activity in the screen, careful toxicological study in experimental animals is necessary in order to define the approximate safe dosage for man and to characterize any toxic reactions that might be observed when the agent goes into clinical trial. This type of data is particularly important in the case of anticancer compounds, which are usually extremely toxic and often damage some types of normal cells almost as much as cancer cells. Preclinical pharmacological testing facilities for the determination of acute and chronic toxicity, side effects, or other results, have been established at the Food and Drug Administration laboratories; furthermore, several laboratories have been set up to study physiological disposition, excretion, metabolism, development of resistance, and mechanism of action—the latter often by means of radioactive tracers—to provide a better basis for the rational selection of compounds for future study.

The following animal studies are usually conducted:

1) Acute toxicity (LD50), both single dose and repeated dose schedules, in two or more species by oral and parenteral routes.

2) Subacute toxicity in rats and dogs (or in some cases monkeys) by a suitable route of administration, for periods up to three months. Several dosage levels are employed to determine the maximum-tolerated levels. These tests include:

a) Periodic hematological examination of these animals, with the certainty that periods as short as one to two weeks from the onset of treatment are included.

b) Periodic blood chemistry, including abnormal pigments, blood sugar, nonprotein nitrogen, and others.

c) Histological examination of the indicated organs and tissues with observation of organ weights at autopsy.

3) Pharmacodynamic action in both unanesthetized and anesthetized animals, with particular emphasis on the cardiovascular, endocrine, excretory, and autonomic and central nervous systems. Other organ or tissue systems are included where indicated.

4) Absorption, tissue distribution, metabolism, and excretion of certain compounds as indicated from other work.

5) Irritation and sensitization properties of preparations of the agent with emphasis on developing the most suitable pharmaceutical preparation.

Human Pharmacology

Before a safe, accurate, and meaningful clinical trial can be undertaken, a preliminary examination of the toxicity of the agent in man must be made in order to determine the safe maximum dose and best dosage schedule, the optimal pharmaceutical preparation of the agent, and the side effects most likely to occur. Such data also make possible the development of antidotal measures in the event of an overdosage and suggest what drugs may be contraindicated for concurrent use. These studies are undertaken in medical centers only after careful planning by the pharmacologist and clinician.

Clinical Trial

When a compound has shown promise in the laboratory and when it has passed the requirements imposed by the toxicological and pharmacological studies, it is ready for clinical trial.

Although any curative or unusually effective treatment will be readily detected, for the present, meticulous clinical trials are essential, because only compounds of marginal activity are usually available for testing—compounds that relieve discomfort, reduce the size of large neoplasms, extend life, or in some way modify the manifestations or the course of neoplastic disease. But it is necessary to know whether a proposed therapeutic agent actually causes a change in the disease and, if so, the consistency and duration of the effect and its mechanism of action. Satisfactory answers to these questions require precise and established laboratory and clinical procedures.

Clinical evaluation of active compounds is beset with many difficult problems. It is exceedingly expensive, trained manpower is in very short supply, and the techniques of clinical investigation are not as precise as they might be. The situation is even more difficult because of the urgent need and constant pressure to do something for the hundreds of thousands of patients dying of advanced cancer. This makes it extremely difficult to evaluate new compounds in a satisfactory manner. The moment a new drug shows activity in man, public and professional pressure is exerted to bring the compound into general use before careful studies can be completed. This, in turn, creates pressure to answer a great many different technical questions, and the tendency is to try to set up studies that will answer all questions at once. The data that are collected by the individual clinic tend to be inconclusive, so each clinic then feels that it must repeat the studies of other clinics. Therefore, much of the data may be almost impossible to interpret even though a great many cases have been studied.

An additional problem in the evaluation of a potential cancer chemotherapeutic agent in man is the lack of objective measurements. Although subjective improvement in symptoms, such as pain, anorexia, or malaise may provide useful evidence of effective therapy in properly constructed and conducted trials, the best criteria are those easily measured, such as diminution or disappearance of subcutaneous masses or of lung metastases as determined by X ray, the recalcification of osteolytic lesions, the de-

crease of peripheral lymphadenopathy, or in leukemia, the return of the bone marrow and peripheral hemogram toward normal.

The cooperative clinical studies stimulated by the Clinical Studies Panel are designed to answer definitively a few questions in each study. The clinical study, in consequence, may serve the purpose of *a*) rapidly and intelligently eliminating materials of little or no use; *b*) determining the types of cancer that are susceptible to the agent; *c*) defining the optimal use of an agent against a specific tumor; *d*) comparing the effectiveness of different agents. In addition, information may be obtained that will (*a*) provide a basis for correlation with animal studies in order to find those animal systems that have a high predicting value for effectiveness in human tumors, and (*b*) provide leads to chemists and theoretical biologists, so that new and different materials can be synthesized and reasonable and fruitful theories of the biology of cancer can be developed.

The development of a cooperative study group under the program is based on encouragement from the Service Center and the spontaneous interest of a group of individuals who feel that certain specific questions require answers and that the number of patients at one medical center is inadequate to provide such answers. Although cancer is common, many of the specific forms are not. Therefore, pooling of patient material is usually necessary for a definitive study. More than ten cooperative study groups have been formed, representing over 100 hospitals located in all sections of the country. Each study group develops an experimental protocol, which defines exactly how the study will be carried out. The protocol includes the criteria for diagnosis, treatment schedule prescribed, measurements to be made, and criteria of response.

Allocation of patients to the treatment and the nontreatment groups (or to additional groups if more than two treatments are under study) is made by random selection so that the two groups will be initially equivalent in those factors thought to be relevant to the inquiry.

Although allocation to groups can sometimes be made successfully by putting patients, as they present themselves, alternately into treatment A and treatment B groups, such a method may lead to biased results when the admission or nonadmission of a case to a trial hinges upon a difficult assessment of the patient and when the clinician involved knows whether the patient, if accepted, will pass to the first or the second group. By such knowledge he may be biased, consciously or unconsciously, in his acceptance or rejection—or through fear of being biased, his judgment may be influenced.

Allocation of the patient to treatment or control groups is kept secret from the clinician until after he has made his decision upon the patient's admission to the study. Wherever possible, the double-blind technique is used. If this is impractical, the results are evaluated in the blind by physicians who do not know which treatment the patient received. In the group, standard record forms are drawn up and uniformity in completing them stressed. Since every departure from the design of the experiment lowers its efficiency to some extent and too many departures

may wholly nullify it, specific measures are taken to secure uniformity, such as frequent meetings and inspection of individual laboratories by each member of the group.

These restrictions would not be necessary if the treatment produced such dramatic effects as penicillin does in lobar pneumonia. Unfortunately, such effects on cancer are the exception rather than the rule. We are often comparing one drug against the other to demonstrate that one causes remissions in 20 percent of the cases as compared to 15 percent for the other.

Such considerations lead us to choose the highly organized, controlled clinical trial of today as the best known means of evaluating potential anticancer agents in man.

End Results

The Service Center has established an end-results program to find the response of cancer patients to total treatment in terms of survival. The data are collected from a group of cancer registries representing a variety of medical institutions in various parts of the United States. Data on some 500,000 cases are now available and it is expected that reports will be received on some 50,000 new cancer patients each year. The registries will submit to the Service Center a duplicate set of IBM punch cards which will contain information on such items as primary site, method of diagnosis, stage of disease, treatment, length of survival, and cause of death, in addition to the usual demographic items.

Plans for three types of special studies are under development: 1) survival experience of untreated cancer patients, 2) review of chemotherapy end results obtained to date, and 3) evaluation of treatment in selected rare forms of cancer.

The Basis for Rational Approaches

Today there are a number of drugs useful in treating certain forms of neoplastic disease. Most of these drugs were introduced into the clinic on the basis of laboratory findings of growth-inhibitory effects in one or more experimental neoplasms. A few of the agents, notably androgen and estrogen, were given human trial on the basis of a hypothesis. Although these drugs are not curative, they can temporarily relieve some of the manifestations of cancer, improve the patients' well-being, and sometimes prolong life. Through study of the mechanisms of action of these drugs and through correlation of their chemical-biological activity, it is hoped that more efficacious drugs can be developed.

Generally speaking, the active drugs fall into three categories: hormones, antimetabolites, and alkylating agents.

Hormones

The alteration of endocrine environment as a major approach in chemotherapy is very interesting. In conjunction with castration, the sex hormones are extremely useful in the treatment of certain carcinomas

that are still hormone dependent. Thus, androgen-control therapy, by means of castration and estrogen administration, has a palliative effect on metastatic carcinoma of the prostate and breast in the male. Inoperable mammary cancer in premenopausal women is treated with castration and androgens. Estrogen therapy in postmenopausal women sometimes achieves subjective improvement for the patient. The adrenal or adrenocorticotrophic hormones, ACTH or cortisone, have limited therapeutic use in lymphoma and leukemia.

Studies are now in progress to discover more active steroid analogues with fewer and less severe side effects; for instance, dehydrocortisone appears to be a more satisfactory agent than cortisone. Another approach is the production of hormonal imbalances by removal of such endocrine glands as the adrenals and pituitary. The role of the several pituitary hormones, the thyroid hormone, and the pancreatic secretions in tumor growth has also come under recent examination. Thus, efforts are being made to alter the physiology of the host in a variety of ways in order to make it a less favorable site for the growth of cancer.

Polyfunctional Cytotoxic Agents

The cytotoxic agents are general cell poisons and consequently have clinical limitations because they affect both normal and malignant cells. They are also called "alkylating" agents because they introduce alkyl groups in place of hydrogen into organic molecules, and "radiomimetic" substances because they produce cellular damage similar to that caused by X radiation. At the present time the sulfur mustards, sulfonic acid esters, bis-epoxides, and ethylenimines are included in this group of agents.

The historical development of the cytotoxic agents currently used for clinical cancer studies began with sulfur mustard, synthesized in 1854, and successfully developed for use as a war gas during World War I. In 1931 it was used clinically for the treatment of localized lesions of skin cancer. Shortly thereafter the aliphatic nitrogen mustards were discovered, and they were found to be better cytotoxic agents, with a selective action on rapidly proliferating cells and a marked effect on lymphoid tissue. Clinical studies with these compounds in the treatment of neoplastic diseases of the lymphoid tissue were initiated at Yale University in 1943. The aromatic nitrogen mustards, which are orally effective antileukemic compounds, were developed after a systematic investigation by the Haddow group and currently are on clinical trial. More recently, the cellular specificity of certain antimalarial drugs has been utilized as a basis for synthesizing potentially more selective alkylating agents. An example is chloroquine mustard.

Although it is known that most alkylating agents are polyfunctional compounds the active groups commonly being the ethylenimino, bis(2-chloroethyl)amino, and methanesulfonoxy, their exact mechanism of action is not known. The theory that enzyme inactivation is responsible for the characteristic effects resulting from therapy with alkylating agents has not been fully substantiated. Other theories are: that the

linkages formed by the intra- and intermolecular reactions of the agent with the nucleoprotein of the chromosomes prevent their separation and thus interfere with the mitotic process; that polymers formed from the various cytotoxic compounds are responsible for their activity; that polymers cause chromosome damage with inhibition of mitosis and chromosome breaks similar to those produced by X rays. The biochemical and cytological evidence implicating the chromosome, a complex nucleoprotein, as the cellular target of these compounds is becoming more extensive.

In general the drugs in this group of anticancer agents have selective toxicity for rapidly proliferating cells, such as those of the hematopoietic system, the intestinal tract, and the gonads. Their hematological effects are characterized by varying degrees of hematopoietic depression. The toxicity of the alkylating agents to the normal marrow prevents adequate dosage in many cases and gastrointestinal disturbances are often seen. The agents are capable of inducing mutations, causing chromosome abnormalities, inhibiting the growth of transplanted animal tumors, and are carcinogenic.

Some of the more commonly used alkylating agents are HN_2 (2,2′-dichloro-*N*-methyldiethylamine hydrochloride), TEM [2,4,6-tris(1-aziridinyl)-*s*-triazine], TEPA [tris(1-aziridinyl)phosphine oxide], thio-TEPA [tris(1-aziridinyl)phosphine sulfide], nitromin (2,2′-dichloro-*N*-methyldiethylamine *N*-oxide hydrochloride), Myleran® (1,4-butanediol dimethanesulfonate), and chlorambucil [4-{*p*-[bis(2-chloroethyl)amino]phenyl}butyric acid].

Antimetabolites

The antimetabolite concept in chemotherapy was established with the discovery by Woods, in 1940, that *p*-aminobenzoic acid (metabolite) would reverse the antibacterial action of the sulfa drugs (antimetabolite). Subsequent biochemical research demonstrated that if the growth-inhibitory action of an agent is reversed by a metabolite, it can generally be assumed that the inhibitor is blocking an essential sequence of events involving the metabolite. The first practical application of this principle in cancer chemotherapy occurred in 1948 when Farber and his associates used folic acid antagonists for the treatment of leukemia. The encouraging results stimulated research on the biochemistry of folic acid and the search for other anticancer compounds based on the antimetabolite principle. Ultimately, purine and pyrimidine derivatives were found which are both folic acid and purine antagonists. Evidence has accumulated in recent years that the folic acid antagonists prevent cells from using single carbon atoms for the synthesis of several amino acids and also prevent the use of these carbon atoms for building purines and pyrimidines, essential constituents of nucleic acids.

The importance of nucleic acids in the growth process of cells makes the inhibition of their synthesis a logical point at which to attack the cancer cell. Chemotherapy with purine antimetabolites is based on the

rationale that differences in the anabolism of polynucleotides exist between normal and cancer cells. Thus far, however, antagonists with anticancer activity are not completely selective in their action; they also affect normal cells.

Clinically, the most effective folic acid antagonists to date have been the 4-amino derivatives of folic acid, aminopterin and methotrexate (amethopterin). *In vitro* and *in vivo* studies have demonstrated convincingly that these compounds prevent the conversion of folic acid to citrovorum factor. The end result is the disruption of cellular metabolism by the establishment of a metabolic block in the intracellular pathway to purines and pyrimidines.

Aminopterin and amethopterin are indicated for the treatment of acute leukemia, particularly the acute lymphoblastic form. They are most effective for the disease in children, less so in adults, with about 50 to 60 percent of the treated children experiencing a remission of from two to eight months' duration. On continued treatment the disease ultimately becomes resistant to folic acid antagonists, and other therapy is then required. The drugs are administered orally. Toxic manifestations, which may occur slowly, include abdominal cramps, diarrhea, and hemorrhage, and these can usually be controlled by regulation of the dose. The antifolics are ineffective for the treatment of chronic leukemias, lymphomas, metastatic carcinomas, or sarcomas.

Of the numerous purine antagonists, 6-mercaptopurine has been most extensively studied in experimental animals and in the clinic. This drug produces remission in children with acute leukemia, both the untreated forms and those that have become resistant to therapy with amethopterin and cortisone. Also given orally, its chief toxic effect is on the bone marrow. 6-Mercaptopurine is ineffective in chronic lymphocytic leukemia, multiple myeloma, Hodgkin's disease, and other metastatic carcinomas and sarcomas. 8-Azaguanine, 2,6-diaminopurine, and 6-chloropurine are more recent analogues. Also of current interest in the area of purine antagonists are the pyrazolo(3,4-*d*)pyrimidines, which have some tumor-inhibitory activity in animals.

The mechanism of action of the various purine and pyrimidine antimetabolites is not fully understood at the present time. The ability of folic acid or citrovorum factor to reverse the effects of the antifolic compounds, in all test systems, has been established; however, the reversal of the purine antimetabolites by certain purines has been possible to a large degree only in microbiological systems. Nevertheless, tracer studies indirectly relate these antimetabolites to nucleic acid metabolism.

There are a number of other metabolic growth processes that are as important as those involving nucleic acid biosynthesis. Attempts to interfere with these other pathways by means of antimetabolites have led to some interesting vitamin and amino acid antagonists which eventually may prove to be of clinical value. The concentrations of certain vitamins, particularly the members of the B complex, are lower in cancerous than in normal tissues. This observation prompted the study of a number of

vitamin antimetabolites with the hope of finding a selective chemotherapeutic agent. Substituting a coenzyme group that is a structural analogue of the natural one may result in a loss of enzyme function and an inhibition of essential metabolic reactions. Some of the members of the B complex for which antagonists have been prepared are riboflavine, vitamin B_6, and vitamin B_{12}.

A number of amino acid analogues have been prepared with the hope that they would be competitive antagonists for an essential amino acid in the tumor. In addition, analogues that would prevent the utilization of serine and methionine may block pathways of nucleic acid synthesis, which are more important to the cancer cell than to the normal cell. An example of an amino acid antagonist is *dl*-ethionine, the ethyl analogue of methionine. The possibility of attacking the cancer cell's metabolism simultaneously at several different points has led to a number of studies on combination therapy. Cells resistant to one drug may be susceptible to another and combination therapy may wipe out all the cells at the start.

Antibiotics

Of all areas now under study the largest number of potentially active compounds have been found in the antibiotic culture filtrates, or "beers." Approximately 1 percent inhibit tumor growth in mice, and upon retest and refermentation, the positives still represent 1/4 to 1/2 percent.

The theoretical premise for testing "beers" is based on the fact that microorganisms and plants have the ability to synthesize compounds with unusual structures and biological activities. The "beers," available as by-products from the extensive industrial search for better antibiotics, are mixtures of literally thousands of compounds, many of which are not available from any other source. However, although the activity rate is high, there are countless problems concerned with isolating the active compound and making it available for further work. For instance, if a "beer" shows low apparent activity, it is difficult to determine whether this is due to a small amount of a highly active compound or to a large amount of a compound with low activity. There are difficulties concerned with concentration and often the fractions become so highly diluted that the active compounds can't be picked up in mouse tests and are therefore missed. For these reasons, much work is needed on the development of methods of recognizing active compounds without the expenditure of large amounts of material.

A number of antibiotics have been studied including azaserine, DON, actinomycin C and D, puromycin, amicetin, and sarkomycin (2-methylene-3-oxocytobutane-1-carboxylic acid). Azaserine, derived from a streptomycete, has been shown to act as a glutamine antagonist in the pigeon-liver system and, as such, interferes with purine biosynthesis. Combined with 6-mercaptopurine, azaserine is under trial in children with acute leukemia. The synergistic effect produced by this combination in animal tumors lends support to the idea of sequential blockade as a means of more effective cancer therapy.

DON was isolated from an unidentified streptomycete and is structurally similar to azaserine. It interferes with the *de novo* synthesis of purines.

Actinomycin C was isolated from *Streptomyces chrysomallus* and actinomycin D is related to it both chemically and biologically. The actinomycins all possess a chromophoric ring structure linked to a polypeptide moiety. Actinomycin C has been used in Hodgkin's disease and other lymphomas, while actinomycin D shows some promise in children with Wilms' tumor.

Puromycin, isolated from *Streptomyces albo-niger*, has shown activity against experimental tumors but no significant action against a variety of human cancers. However, the aminonucleoside derived from it is more promising.

Amicetin, a cytosine-containing antibiotic whose structure is only partially elucidated, has had limited, inconclusive application in the treatment of children with acute leukemia.

Sarkomycin is effective against the Ehrlich ascites tumor in mice. It may function as an alkylating agent but structurally it bears little resemblance to other anticancer compounds.

The Role of Basic Research

Although the search for effective cancer chemotherapeutic agents has been largely empirical, the importance of the solid foundation laid down by basic research cannot be overemphasized, for it is only through the vast amounts of basic data in all disciplines of science that an empirical program can function.

The support of basic research fits best into a research-grant framework. In general, only basic research most applicable to chemotherapy is supported under the program. However, every effort is made to give ample support to basic research either in the non-chemotherapy grants program of the National Cancer Institute or in other programs of the National Institutes of Health.

Basic research being carried out under the grant-supported program of the Service Center includes: studies on mechanism of action of agents; the search for agents with general inhibitory activity against neoplastic cells; and studies of the fundamental physical and chemical characteristics of cells, in the hope that eventually differences between normal and neoplastic cells will be found.

Services Offered

Since few research programs in cancer chemotherapy are self-sufficient and most need more facilities and a greater variety of technically trained personnel than are available to them, the Service Center offers the following services in addition to the support of basic research, initiation of a screening program, and the stimulation of clinical studies:

1) Location and procurement of adequate amounts of needed compounds for studies in cancer chemotherapy.

2) Procurement of labeled compounds for research purposes, provided the investigators have been approved by the Atomic Energy Commission to use such materials.

3) Arrangements to have compounds screened as anticancer agents.

4) Arrangements for pharmacological studies on compounds showing enough promise in animal screening to be interesting for possible human trial.

5) Arrangements for clinical evaluation of those compounds exhibiting adequate activity in screening tests, provided suitable pharmacological data are available.

6) Arrangements for interinstitutional cooperative clinical studies for large-scale evaluation of compounds when preliminary clinical results indicate that such studies would be justified.

7) Provision of suitable technical consultation or information on problems relating to cancer chemotherapy.

8) Information on possible sources of financial assistance for research, training, or travel related to cancer chemotherapy.

9) Communication with research workers and institutions interested in cancer chemotherapy in other parts of the world.

Other services are the establishment of a documentation center for information on cancer chemotherapy. Compounds are indexed for correlation of chemical structure and anticancer activity, and a bibliography of the literature on cancer chemotherapy is being maintained and published.

A publication, *Current Research in Cancer Chemotherapy*, is issued by the Committee on Chemotherapy of the National Advisory Cancer Council in cooperation with the program sponsors and is printed by the American Cancer Society. It is published to provide an informal compilation of information for investigators in the field of cancer chemotherapy and is available, without charge, upon request to the Service Center.

Probable Trends in the Immediate Future

Industry

In a drug-development program of this magnitude, the help and cooperation of industry, with its compounds, special skills, know-how, and facilities, is of primary importance. In the pharmaceutical industry a lead developed in the laboratory can be followed rapidly, thoroughly, and efficiently to the stage of a useful product available to the practicing physician. Within the past year, thanks to the efforts of the Industry Subcommittee, this cooperation has grown remarkably. The part that industry can play includes:

1) Supplying large stocks of untested new chemicals, which serve as sources of new leads.

2) Supplying antibiotic "beers" in very large numbers.

3) Providing facilities, know-how, and integrated teams of specially

trained personnel to develop and follow up leads. This involves activities such as *a*) screening of substances for new leads; *b*) synthesis and comparison of series of new chemicals closely related to those that have been found active; *c*) isolation, purification, identification, and production of antibiotics from the crude beers; *d*) adaption of test-tube techniques for use in large-scale testing or production; *e*) batch production, formulation, and toxicity testing of agents for clinical trial.

Such industrial participation accelerates the acquisition of new leads, permits rapid and thorough exploration of existing leads, and assures that as the usefulness of a drug is demonstrated, it becomes available quickly for general medical use.

It is expected that the National Cancer Institute will enter into research and development contracts with a number of industrial firms. In order to assure effective collaboration, the Public Health Service is developing policies and procedures that will generate and maintain both confidence and enthusiasm on the part of industry.

In the future we expect that some provision of in-plant biological testing will be desirable for expeditious handling of active isolation of natural products.

In certain fields, it may be necessary to provide Federal support to those industrial research projects that are likely to lead directly to the conception and invention of new products. We believe that when such support is provided on a substantial scale, it will be necessary to safeguard the Government's equity in such discoveries and inventions by reserving certain specific rights to the Government.

We are confident that these problems will be resolved eventually and look forward to the time when industry-government cooperation is as effective in the pharmaceutical area as it is in some of the defense areas.

Antibiotics

It appears inevitable that the immediate future will bring an intensive exploration of antibiotic culture filtrates as sources of compounds for clinical trial.

Steroids

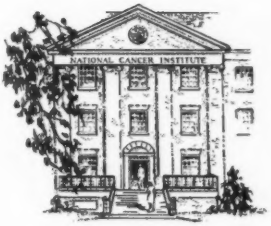
Plans for clinical trials of a rather large number of hormonally active synthetic steroids are nearing completion. Pilot-plant facilities for production of adequate batches of chemicals are in preparation. The next few years should improve the opportunity for intelligent correlation of chemical structure with clinical activity.

Conclusions

Although the chemical control of cancer has not yet been achieved, the outstanding progress in chemotherapeutic control, within a relatively short period of intensive research, is indicative of the promise shown by this field. Just ten years ago, less than 5 percent of children with acute

leukemia lived as long as one year. Today, the one-year survival rate has been raised 50 percent by the use of chemicals and adjunct therapy.

The past years have been a period of preparation, acquiring knowledge, organizing research teams, and refining instruments and techniques. Now, with the impetus given this field by Congress, it has been possible to bring together the pharmaceutical industry, research organizations, private investigators, and the United States Government, each contributing their varied skills and resources to implement an effective cooperative national program.



Thirteen Questions:

Some Historical Outlines for Cancer Research

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The best prophet of the future is the past—Lord Byron

I. 1802

IN the July 1806 issue of the *Edinburgh Medical and Surgical Journal*, there appears a reprint of thirteen questions and comments compiled four years before by the Medical Committee of the Society for Investigating the Nature and Cure of Cancer.

About all that is known of this London group is contained in the reprint. Its illustrious medical committee included John Abernethy, John Hunter's pupil and his successor as Surgeon to St. Bartholomew's Hospital; Matthew Baillie, nephew of the Hunters and author of *Morbid Anatomy;* Robert Willan, founder of British dermatology; and John Hunter's brother-in-law, Everard Home. The Committee's report antedates the discovery of the cell, and hence all cellular pathology, by well over thirty years.

The Queries speak for themselves. Except for some now-quaint-sounding expressions and the antiquated print, most of them can still be asked in the same form. Lucid, succinct, and eschewing theorizing, their relevance after a century and a half serves to underline the slow pace of our progress.

The Committee's questions and comments are primarily clinical in their orientation. Hunter and his school were noted for their interests in comparative anatomy and comparative pathology, but the group was not certain ". . . whether brute creatures are subject to cancer, . . ." It urged investigation of this topic, since it ". . . may lead to much philosophical amusement and useful information; . . ."

The Committee has little to say, or to suggest, about treatment, except to record that ". . . all the medicines and methods of treatment hitherto proposed and tried have been unavailing." But one of the reasons for suggesting the study of precancerous alterations is that perhaps the disease might be "extinguished" in an early stage.

The Committee comes to grips with the problem in its first question: "a precise definition, or a competent description" of cancer. It would approach this through a study of alterations ". . . preceding that more obvious change which is called cancer; . . ." and this not only through

morphologic observations but ". . . by a chemical analysis of the component parts; . . . conducted through the different stages; . . ."

We can, perhaps, answer with some assurance the fourth and fifth questions, and the last four questions. At least we can find answers that would be acceptable to most of our contemporaries, although they may sound somewhat strange in yet another century. But a generally acceptable answer would be difficult to devise for the seventh question: Can cancer be regarded as a local disease? Or the sixth: Are all cancers "exactly the same disease"? And can we even phrase more explicitly questions eight and nine, which ask investigation of environmental influences and the influences of the host factors in the development of cancer? How much has been added to our understanding of the neoplastic process by substituting other words for "temperament," which was even then admitted to be "without any precise meaning"?

THE

EDINBURGH

MEDICAL AND SURGICAL

JOURNAL:

EXHIBITING

A CONCISE VIEW

OF THE LATEST AND MOST IMPORTANT

DISCOVERIES IN MEDICINE, SURGERY, AND PHARMACY.

1806.

VOLUME SECOND

EDINBURGH:

PRINTED FOR ARCHIBALD CONSTABLE & COMPANY, EDINBURGH;
AND JOHN MURRAY, LONDON; AND GILBERT
& HODGES, DUBLIN.

1806.

382 *Inſtitution for Inveſtigating the Nature of Cancer.* July

The MEDICAL COMMITTEE of the SOCIETY for INVESTIGATING the NATURE and CURE of CANCER, conſiſting of Drs Baillie, Sims, and Willan; Meſſ. Sharpe, Home, Pearſon, and Abernethy, and Dr Denman, Secretary, circulated in 1802 a ſet of Queries for obtaining information regarding theſe. Since that time they have been republiſhed, with Obſervations explanatory of their object. In reprinting a *Brochure* of ſo much intrinſic value, we hope both to preſerve it, and to forward the views of ſo laudable an Inſtitution.

EVERY perſon muſt be ſenſible of the various difficulties attending the eſtabliſhment of a new inſtitution, and of the much greater and more numerous difficulties which beſet our firſt ſteps in the acquiſition of knowledge on a ſubject of which, it may be ſaid, we are even at this time totally ignorant *. But, in order to form a baſis of inquiry, in which the nature and cure of cancer, it is preſumed, may be purſued with all the advantages of reaſon and experience, the Medical Committee very early drew out and diſtributed the following queries, for the conſideration not only of the correſponding members, but of all medical men, to whom opportunities of anſwering them might, by ſtudy or by accident, occur. A ſatisfactory anſwer to any one of theſe queries would, in itſelf, be of great importance, and might probably lead to an explanation of others. It is therefore earneſtly requeſted, if any new obſervation or diſcovery reſpecting cancer ſhould be made, that it may be communicated to the ſecretary of this inſtitution; and, if any progreſs in the inveſtigation of the nature and cure of cancer be made by or imparted to them, it will, without delay, be laid before the public by the Medical Committee. It may be neceſſary to obſerve that the promoters of this inſtitution have never entertained the idea of creating the jealouſy, or of interfering with the intereſts, of thoſe who are engaged in inſtitutions of a ſimilar kind; their intention being ſolely that of co-operating in the laudable endeavour to leſſen the maſs of human miſery, by calling for the aſſiſtance of others, and by exerting themſelves to obtain a remedy for a moſt painful and dreadful diſeaſe, againſt which all the medicines and methods of treatment hitherto propoſed and tried have been unavailing.

The queries above-mentioned are expreſſed in as plain terms as the nature of the ſubject would allow; but it has been thought that ſome benefit would accrue from a ſhort comment or explanation of the aim and purport of each query in the following manner:

QUERY 1ſt.—*What are the diagnoſtic ſigns of cancer?*

It is very much to be wiſhed that we had an exact definition of cancer, thoſe of the noſologiſts being very imperfect and inſufficient. It has accordingly happened that a diſeaſe, which has been denominated

* It is ſcarcely neceſſary, in this place, to refer the reader to an excellent Treatiſe on Cancer, by Mr Pearſon, ſurgeon of the Lock Hoſpital.

nated cancer by one medical man, has not been allowed to be ſuch by another; and painful and hazardous operations have been performed by ſome, which were not thought neceſſary, or likely to be ſucceſsful, by others. Hence an opening has alſo been made for falſe pretenſions and impoſitions; and, though no perſon converſant in practice thinks that a true genuine cancer was ever cured, there is an abundance of caſes in which cures of this diſeaſe are aſſerted with the greateſt confidence. If a juſt and exact definition of cancer cannot yet be formed, we muſt be ſatisfied with ſuch a deſcription as a correct hiſtory of the diſeaſe will afford. This, it appears, has never yet been judiciouſly and accurately done; though it would probably enable us to diſcriminate the various forms of the diſeaſe, and its diſtinction from other diſeaſes. Till, therefore, a preciſe definition, or a competent deſcription be formed, it will be incumbent on us to mark all the ſymptoms peculiar and incident to cancer, and the order in which they ariſe, together with the varieties of this and ſimilar diſeaſes, and the effects of the medicines which may be tried under all the different circumſtances, that we may be able to ſay ſomething more ſatisfactory than that it ſeems to us to be cancer; or that it is cancer, becauſe it is an indurated, painful, and unequally enlarged gland, terminating in ulceration; or that every ulcer, in certain parts, which reſiſts the common modes of treatment, or methods of practice, is to be regarded as cancerous. It is much to be wiſhed that we may no longer be deceived by ambiguous words and phraſes, or conſider them as conveying to us any eſſential or practical knowledge.

QUERY 2d.---*Does any alteration in the ſtructure of a part take place, preceding that more obvious change which is called cancer; and if there be an alteration, what is its nature?*

It might firſt be aſked, Does any diſpoſition to cancer in any part take place previouſly to any phyſical alteration or change of ſtructure in the part? or are there any ſymptoms, local or conſtitutional, which denote that cancer is about to be formed? Then we may conſider how the firſt alteration in the ſtructure of a part diſpoſed to become cancerous is to be diſtinguiſhed from the ſtructure of a part perfectly ſound and healthy, or from the ſtructure of parts diſpoſed to other diſeaſes. To ſuch queſtions it might be anſwered, by the aſpect; by the touch; by diſſection; by corroſion of parts; by maceration; by boiling, or otherwiſe ſubjecting them to the operation of fire; by a chemical analyſis of the component parts; by putrefaction; and by all the various methods uſed to detect the ſtructure and other qualities of any part generally, or of its diſtinct component parts. Nor ſhould this inveſtigation ceaſe with the beginning diſeaſe, but it ought to be conducted through the different ſtages; and this ſubject is now ſo open, both with regard to experiment and to the correction of what has been before ſaid and done, that it is ſcarcely poſſible

poſſible for any one to employ their thoughts upon it without improvement.

One great conſequence of obtaining an anſwer to this query would be, that though we are unable to cure cancer in an advanced ſtage, we might extinguiſh the diſpoſition to it, or ſuppreſs it completely in an early ſtage, whether the diſpoſition or the progreſs conſiſt in increaſed or new action of a part, or in a change of ſtructure.

Some pains have been taken to diſcover, by the properties of the diſcharge from cancer, the nature of the diſeaſe. Through a long ſeries of writers, from the time of Galen, *atrabilis* was conſidered as the cauſe of cancer; ſome thinking that it was of an acid, and others that it was of an alkaline quality; and thoſe of each perſuaſion have attempted to cure the diſeaſe by oppoſite remedies and applications, with different effects, perhaps, but eventually with the ſame termination. It is not, however, yet aſcertained that the diſcharge from cancer is different from ſimilar diſcharges, whether ſerous, ſanious, or purulent, made from parts affected with totally different diſeaſes.

QUERY 3d.—*Is cancer always an original and primary diſeaſe; or may other diſeaſes degenerate into cancer?*

This is a queſtion which has been very much diſputed; at leaſt there have been many different opinions concerning it. It does not imply that all the changes which take place from the commencement of the ſame diſeaſe, through its progreſs to the time when it is acknowledged to be indubitably a diſeaſe of a certain kind, ſhould bear an exact or cloſe reſemblance: but it relates to the abſolute change in the eſſence of one diſeaſe to that of another, with which it had originally no reſemblance or affinity. We muſt, therefore, leave this query to be determined by future experience and obſervation; and if the latter clauſe of it ſhould unexpectedly be decided in the affirmative, we muſt then inquire what kind of diſeaſe, and under what circumſtances of the part, or of the conſtitution, there exiſts ſuch aptitude to degenerate into cancer.

QUERY 4th.—*Are there any proofs of cancer being an hereditary diſeaſe?*

Whether cancer or any other diſeaſe be, ſtrictly ſpeaking, hereditary, has, like many other opinions, been poſitively aſſerted, and as poſitively denied. Whether children born of cancerous parents be more liable to cancer than others, from any ſtructure or organization of the body, or any rooted principle of the conſtitution, may, by attentive obſervation, be diſcovered; and, if it ſhould be ſo proved, we might be led to the prevention of cancer by medicine, by well-regulated diet, or a circumſpect manner of education, and of living. If it be proved, on the contrary, that cancer is not hereditary, the minds of many would be relieved from the diſtreſs of perpetual apprehenſion.

QUERY

QUERY 5th.—*Are there any proofs of cancer being a contagious diſeaſe?*

This query certainly requires ſome explanation. Does it imply a poſſibility of cance being conveyed from one perſon to another by the breath, as in the hooping-cough, and, as ſome have ſuſpected, in conſumption? or by effluvia exhaled from a body afflicted with this diſeaſe, as in infectious fevers? or, by the breath paſſing over an ulcerated ſurface, as in cancer of the mouth or lip? The opinion of cancer being contagious having been advanced, it is become neceſſary to diſcuſs it, as far as we can, by obſervation, by experiments, and by caſual occurrences. Now we are endeavouring to collect all the *incidentia cancro*, the moſt apparently trifling fact, if duly authenticated, ſhould not be ſuffered to paſs without notice, as it may direct us to the knowledge of things of great importance.

QUERY 6th.—*Is there any well-marked relation between cancer and other diſeaſes? If there be, what are thoſe diſeaſes to which it bears the neareſt reſemblance in its origin, progreſs, and termination?*

Whether there be any relation or affinity between cancer and other diſeaſes acknowledged not to be cancerous, as is the caſe with all unproved aſſertions, has been by ſome affirmed, and by others denied. The ſecond part of this query is equally unſupported and maintained. Some have been aſſured of the affinity between cancer and ſcrophula, and others of that between cancer and ſyphylis: but neither of theſe opinions have been proved or well ſupported by a juſt ſtatement of facts, by regular induction, nor by any collateral circumſtance accompanying methods of cure, or the uſe of any particular medicine. Many of the terms given to diſeaſe by the ancients ſeem not to have been preciſely uſed; yet they made ſome diſtinctions of ſimilar diſeaſes, with which few people at the preſent time ſeem to be exactly acquainted. For inſtance, by Cancer, or Carcinoma, they meant a ſpreading ulceration of a ſchirrous tumour; by the term Lupus, an inveterate and corroding ulcer; and, by *Noli me tangere*, probably they meant to denote in general what the words imply; tumours, which, while they remained eaſy and at reſt, ſhould not be diſturbed. They gave alſo names according to the part affected, but without any difference in the nature of the diſeaſe. But more particular inquiry ſhould be made on this part of our ſubject; for Mr Home has given a very intereſting account of his having removed large portions of the tongue, in diſeaſes of that part, which were allowed to be cancerous. Is it proved that cancer of the breaſt is exactly the ſame diſeaſe as cancer of the tongue, or that of the uterus? or that, in every caſe of cancer, in any part, the ſame method of treatment will be proper? The diſtinction of ſimilar diſeaſes is very neceſſary, becauſe medicines, which may be of ſervice in one of theſe, may be injurious in another. Let us hope that, when preciſe diſtinctions are made between cancer and reſembling diſeaſes, and between the various kinds of cancer, appropriate and efficacious methods of treatment

ment of each diſeaſe will follow, to the great benefit and relief of the afflicted, and to the credit of the profeſſion.

Mr Hey of Leeds, in a late publication, has given an account of a new or hitherto imperfectly deſcribed diſeaſe, which he calls *Fungus Hæmatodes*, which, as it is incurable, we have no better way of claſſing than as a ſpecies of cancer.

Now we are ſpeaking of the terms uſed by the ancients, it will not be amiſs to obſerve that, from the time of Galen to the preſent, there ſeems to have been little or no difference between the medicines given, and the applications uſed, for the cure or relief of cancer.

QUERY 7th.---*May cancer be regarded at any period, or under any circumſtances, merely as a local diſeaſe? Or does the exiſtence of cancer in one part afford a preſumption that there is a tendency to a ſimilar morbid alteration in other parts of the animal ſyſtem?*

An anſwer to this query would be highly important, as it is the *experimentum crucis* of many operations which have been performed for the extirpation of cancerous parts. In cancer of one part, perhaps, all ſimilar and ſympathizing parts may be affected; perhaps the whole conſtitution. A ſurgeon, who is ſaid to have great ſkill and ſucceſs in removing cancerous breaſts, has ſaid, that in many truly cancerous affections of that part, he had found, on examination, that the uterus exhibited marks of the ſame diſeaſe, and that the ſtate of the uterus was his guide in determining him to extirpate or to avoid operating upon diſeaſed breaſts. If the uterus was diſcovered to be affected, he refuſed to perform the operation, having conſtantly found it unſucceſsful under ſuch circumſtances; yet it does not follow that all extirpations of the breaſt will be ſucceſsful, if the *uterus* be free from diſeaſe. When operations fail to remove the whole diſeaſe, which is in ſome caſes impracticable, the ſufferings of the patients are aggravated, and their lives ſhortened, by operations; of courſe they ought not then to be performed. Tumours in the breaſt, of a conſiderable ſize, will often remain in a quieſcent ſtate for many years, even to the cloſe of life, if not diſturbed by injudicious treatment or extraneous injuries, of which the ancients were well aware. It therefore appears as improper to extirpate theſe as it does to ſuffer them to remain, when they begin to be diſturbed, and can be wholly removed. It appears that more caution than has been uſually exerciſed ſeems neceſſary in theſe operations. It is alſo requiſite to decide, by repeated trials, whether the extirpation of cancerous breaſts by the knife or cauſtic be preferable, as far as relates to the operation, or a proſpect of a return of the diſeaſe. In practice, we muſt diſtinguiſh between the extirpation of a diſeaſed part and the cure of the diſeaſe; the latter of which is the object of theſe queries, as many parts which do not admit of extirpation are liable to cancer. Certainly many breaſts, which were not cancerous, have been extirpated by a painful operation, often through the want of ſome criterion of cancer, and ſometimes, it is feared, from motives of ſelf-intereſt, or a cupidity to acquire undeſerved reputation. It is worthy of obſervation *to determine* whether any cancerous ſore in the breaſt, or any

other part, had ever more than one opening, and whether external injuries ever give riſe to cancer, or merely aggravate and put in action a diſeaſe which before exiſted. In the *Lock Hoſpital*, there is at this time a caſe of cancer of the *penis*, apparently occaſioned by external injury alone. The ſame fact has been often aſſerted in cancer of the breaſt.

QUERY 8th.—*Has climate or local ſituation any influence in rendering the human conſtitution more or leſs liable to cancer, under any form, or in any part?*

There is a conſiderable variety in the diſeaſes to which human beings are liable in hot and cold climates, and in damp or dry ſituations, or in thoſe which are low or expoſed. The *Goitre* has not been found, or very rarely, in warm and flat countries, nor the *Yaws* in cold ones. The *Lepra*, of every kind, is infinitely more frequent in ſome countries than in others, and more virulent. With regard to cancer, it is not only neceſſary to obſerve the effects of climate and local ſituation, but to extend our views to different employments, as thoſe in various metals and manufactures; in mines and collieries; in the army and navy; in thoſe who lead ſedentary or active lives; in the married or ſingle; in the different ſexes, and many other circumſtances. Should it be proved that women are more ſubject to cancer than men, we may then inquire whether married women are more liable to have the *uterus* or breaſts affected; thoſe who have had children or not; thoſe who have ſuckled, or thoſe who did not; and the ſame obſervations may be made of the ſingle. The cancer to which chimney-ſweepers are ſubject is known, but not accurately underſtood; and none but fruitleſs obſervations have yet been made upon it, except ſuch as relate to operations.

QUERY 9th.—*Is there any particular temperament of body more liable to be affected with cancer than others? If there be, what is the nature of that temperament?*

The word *temperament* has been often uſed by medical writers without any preciſe meaning. It is here meant to ſignify any native or acquired habit of body, which may diſpoſe to or reſiſt the influence of cancer. Should this query be anſwered in the affirmative, having diſcovered the temperament moſt liable to cancer, we might be led to the prevention of this diſeaſe, as was before obſerved under query the 4th.

QUERY 10th.—*Are brute creatures ſubject to any diſeaſe reſembling cancer in the human body?*

It is not at preſent known whether brute creatures are ſubject to cancer, though ſome of their diſeaſes have a very ſuſpicious appearance. When this queſtion is decided, we may inquire what claſs of animals is chiefly ſubject to cancer; the wild or the domeſticated; the carnivorous or the graminivorous; thoſe which do, or thoſe which do not chew the cud. This inveſtigation may lead to much philoſophical amuſement and uſeful information; particularly it may teach us how far the prevalence or frequency of cancer may depend upon the manners and habits of life. As eſtabliſhments are now formed for

for the reception of ſeveral kinds of animals, and as the treatment of their diſeaſes has at length fallen under the care of ſcientific men, it is hoped that the information here required may be readily obtained. If animals which live only on herbs, and never drink any other liquid than water, prove to be the leaſt or not at all ſubject to cancer, ſuch proof may, in many caſes, become a guide in practice.

Trees and other vegetables are ſubject to diſeaſes which in time deſtroy them, if not remedied by art. They are alſo ſubject to injuries from external cauſes. In both theſe caſes, the conſtitutional powers of the plant are exerted as evidently for its preſervation, and for repairing its injuries, as in animal bodies, and in a manner not unlike what has been obſerved in animals, under the ſame circumſtances.

QUERY 11th.---*Is there any period of life abſolutely exempt from the attack of this diſeaſe?*

With regard to the periods of life when human beings are moſt or at all liable to cancer, it ſeems to be generally admitted to be moſt frequent in old or advanced in age; but this is not ſatisfactorily proved. Nor is it certainly known what is the earlieſt period of life at which cancer has been obſerved to take place; though no caſe of that diſeaſe has yet been noticed before twenty years of age; at leaſt not before the time of puberty, when the parts, moſt frequently affected with cancer, undergo a great and conſpicuous change; ſo that ſome connexion may poſſibly be obſerved between puberty and this diſeaſe. The ſame may alſo perhaps be obſerved at the time of the final ceſſation of the menſes. Among large bodies of children collected together in charity and other ſchools, or of adults in hoſpitals, in convents, and in monaſteries, opportunities of anſwering this query muſt certainly occur. There is, however, at this time, a young woman in the inſtitution with cancer of the tongue. She is in the eighteenth year of her age, full grown, but has never menſtruated. She never had any glandular or ſcrophulous complaint, but was a very healthy girl, till about ten months ago, when a ſlight ulceration appeared on the left ſide and near the middle of her tongue, which is in great part, at this time, deſtroyed. Her teeth are of a jet black colour. Though ſhe muſt of neceſſity ſwallow conſiderable quantities of purulent matter from the ulcerated cancer, her health is, in all other reſpects, perfectly good.

QUERY 12th.---*Are the lymphatic glands ever affected primarily in this diſeaſe?*

This query goes to the very root of inquiry with reſpect to cancer, which has been hitherto ſaid always to originate in the glandular ſyſtem, without diſtinguiſhing, however, the particular ſet of glands. In cancerous affections of the eye, it is believed that the ball of the eye is not primarily affected, but the lachrymal gland. In cancers of the breaſt, the lymphatic glands appear to be affected only in a ſecondary way, when the diſeaſe is making progreſs. It is probable that careful attention to the objects of this query would lead to many new obſervations reſpecting the firſt ſeat, cauſe, and effect of cancer.

QUERY

QUERY 13th.—*Is Cancer, under any circumſtances, ſuſceptible of a natural cure?*

Many diſeaſes and accidents, to which the human body is liable, are cured or repaired by ſome proceſs of the conſtitution peculiarly and admirably adapted to the kind of diſeaſe or accident. The principle of this proceſs, or the proceſs itſelf, has uſually been expreſſed by the term Nature, and, in medical language, more frequently *Vis Medicatrix*. But no inſtance has ever occurred, or been recorded, of cancer being cured by any natural proceſs of the conſtitution. It is not, however, unlikely that the enlargement of a part containing the *corculum*, or firſt principle of cancer, may be in conſequence of a proceſs ſet up by the conſtitution for confining the effects of the diſeaſe to the part where it originally exiſted: thus preventing its ravages or influence upon the conſtitution. When, therefore, an indurated and enlarged part of a truly cancerous diſpoſition begins to inflame and to be diſturbed, the morbid principle may be conſidered as having overpowered the ſhield or barrier formed around it for the defence of the conſtitution. On this principle, trees, when injured by external or other cauſes, ſeem to exude and form an external or adventitious ſupport to ſupply the deficiency of the part weakened or deſtroyed. But this is a ſpeculation with which we are not concerned, and by which we are in no degree whatever to be guided in the preſent inquiry. Facts alone, and thoſe indubitably proved, are in this place to be admitted, till ſuch a number ſhall be collected as will enable us to eſtabliſh, by fair induction, a ſound practice, no longer the creature of preſumption or vain opinions.

In the few inſtances of cancerous parts becoming gangrened, in the breaſt for example, though the whole *mamma*, or a great part of it, has ſloughed away, the ulcer has remained cancerous, and none of the patients have been ſaved. It is a curious fact, and worthy of particular notice, that no perſon with an old ulcer in the leg has ever been known to have cancer, though the ulcer was not ſuſpected to be cancerous. From this obſervation it is probable that iſſues have been ſo often directed, with the view of preventing or retarding the progreſs of cancer.

II. 1902

Exactly one hundred years after the London Committee phrased its questions, E. F. Bashford of Edinburgh submitted a *Scheme for Enquiring into the Nature, Cause, Prevention and Treatment of Cancer.* This was the basic document of the Imperial Cancer Fund, of which Bashford was designated the first director.

Interspaced in Bashford's *Scheme* are almost all of the questions of the previous century, still to be answered. He calls first for statistics to help " . . . to decide whether any form of disease comprised under the term 'malignant' is communicable from one individual to another." and to consider " . . . all alleged causes—heredity, race, climate, soil, etc., and also the reputed increase of cancer."

The *Scheme* also suggests research " . . . to determine if the chemistry of the normal cell shows any divergence from that of the cancer cell which has developed from it." He even mentions liver and hepatoma as desirable materials for the comparative study of the ferments contained therein.

The third chief area of research that is proposed is the experimental production of cancer in animals. The two references to "Sweeps' cancer," suggesting the study of " . . . persistent irritation of different epithelial surfaces in different species of animals . . . . " prophesies the success achieved thirteen years later by Yamagiwa and Ichikawa. Perhaps Bashford's research plans were delayed by his shift of interest to the transplantable tumors of Jensen, with which he was evidently not acquainted at the time he prepared his draft.

Some clinical aspects of cancer research are also outlined briefly in the *Scheme.* A systematic search for "incipient or undetected malignant disease" in autopsy material is suggested, and interest is shown in the study of the spread and metastases of cancer. It is planned to test, "along modern bio-chemical lines," therapeutic sera and the "antagonistic nature of internal secretions."

Bashford's administrative plan is an interesting one, particularly in the present age of large institutes. He wanted a central laboratory and associated workers in other laboratories, the latter perhaps an early version of a grant-in-aid system. But for the central unit his initial requests were modest indeed: " . . . two or three rooms . . . one or two good secretarial assistants, and two or three assistants skilled in microscopical work . . . . " Until 1908 the Imperial Cancer Research Fund did in fact consist of Bashford and Murray and a few interested voluntary associates. How much such a small group could accomplish is documented in the beautiful scientific reports of the Fund.

Among the outstanding contributions of the Fund were the meticulous studies of the biologic and morphologic features of spontaneous and transplanted tumors of mice. These investigations were influential in the general acceptance of animal tumors as neoplasms comparable to those of man and set the pattern for the subsequent course of cancer research.

THIRD SCIENTIFIC REPORT

ON THE INVESTIGATIONS

OF

THE IMPERIAL CANCER RESEARCH FUND.

Under the direction of the Royal College of Physicians of London and the Royal College of Surgeons of England

BY

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and
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Published by the Authority of the Executive Committee.

LONDON:

PRINTED AND PUBLISHED BY

TAYLOR AND FRANCIS, RED LION COURT, FLEET STREET, E. C.

1908.

Vol. 19, No. 2, August 1957
430090—57——13

APPENDIX II.

Draft of Scheme for Enquiring into the Nature, Cause, Prevention, and Treatment of Cancer*.

1. GENERAL NATURE OF THE ENQUIRY AND GENERAL ORGANISATION.

Scope.

The term "Cancer" must be taken to include all malignant new growths, and this conception must be extended to similar diseases in animals, both for studying the subject in them, and in relation to the possibility of transmission to man.

Character Constituting Malignancy and Spread.

The investigation must further include the conditions favourable to spread in the body and the other features of malignancy, since these constitute the serious aspect of cancer as distinct from innocent growths. Any change which would prevent the acquisition of malignancy, or which would hinder such spread, would be of very great value.

Statistics as to Incidence. General Causes.

The enquiry should include the compilation of accurate statistics bearing on all the conceivable conditions possibly associated with the incidence of the disease.

*Printed from the copy officially filed.

The Possibility of Different Causation in Different Groups; Separation of Special Groups, Some Possibly Parasitic.

The study of all new growths in order to classify them, and to distinguish the various form which at present may be grouped together as malignant growths is important. It might thus be possible to eliminate some types which may be found to be of definite, and possibly of very diverse parasitic origin. This will constitute an important feature of the work to be done.

Experimental Production of "Cancer."

It will be necessary to attempt to produce new growths in various ways, or to attempt so to modify non-malignant growths that they become malignant.

Bio-chemical and Physiological, Possibly Including Therapeutic Substances.

Investigations along modern bio-chemical lines, with consideration of the conceivable production of cytolytic, agglutinative, antagonistic, perhaps therapeutic sera, and the possible occurrence and antagonistic nature of internal secretions, etc., will demand very serious attention.

The organisation will consist of:—

(1) A central bureau and laboratory for general direction of the undertaking, for study, research, control of work being done and of the results obtained elsewhere, and for the summarising of results and the interpretation of statistical investigations by those working there.

(2) Associated workers carrying on special parts of the investigation in their own laboratories or hospitals, etc. There would thus be an attempt to utilise so far as possible existing laboratories, and also skilled workers, who occupy other important positions.

(3) Other persons from whom statistics might be collected, etc.

The ultimate greater development of the experimental side of the enquiry being borne in mind, the control work might be begun by classifying all that is grouped under the term malignant disease, and by collecting statistics.

At the outset two or three rooms giving accommodation for the director, one or two good secretarial assistants, and two or three assistants skilled in microscopical work would be required.

At a subsequent date the investigation will in all probability require much more extensive laboratory accommodation, and it will be necessary to obtain some place where animals can be bred and kept, and probably a farm will be required.

Of the skilled assistants, one should if possible be a trained veterinary surgeon who, apart from his special duties in connection with the important veterinary aspects of the research, would at a later date be invaluable in regard to supervision of animals destined for research purposes.

In an enquiry which may ultimately require the keeping of many animals, both of the larger forms, e.g., horses, anthropoid apes, etc., proper attention to the hygiene of the animals would be essential; apart from the experimental importance of being able to exclude previous infection, ultimately a proper farm with efficient means for isolation and perhaps for the breeding of animals would be necessary.

A second assistant should be specially detailed to assist in the bio-chemical researches, and should have had a proper chemical training, if possible; also a training in physiological chemistry. A third assistant should preferably be a man skilled in zoological and general biological enquiry. All assistants should be skilled in microscopical and general histological technique.

At a later date a larger expert staff will probably be found necessary. In the compilation of statistics the services of a trained actuary would be almost essential for a time.

The enquiry must start at selected points and be allowed to develop itself in the hands of those conducting it along those lines which the experience accumulated, will in natural course dictate. The proceedings must therefore be cautious, and conducted on the very widest basis. At present we possess no knowledge which justifies limiting the enquiry in any special direction, but no reasonable line of special enquiry should be discouraged.

The scope at the outset being so very wide, the work should primarily be directed to attempting to define the field of legitimate enquiry, and within the shortest time possible attempting to focus the efforts on a rational research for the causal factor or factors. This limitation may best be obtained within a reasonable period by following out systematically various lines of enquiry at the same time:—Statistical, histological, chemical; pertaining to cancer in various human races, animals, plants (?), and with consideration of all alleged causes—heredity, race, climate, soil, etc., and also the reputed increase of cancer.

2. RECOMMENDATIONS BEARING ON SPECIAL LINES OF ENQUIRY WHICH MAY BE DIVIDED INTO STATISTICAL, EXPERIMENTAL, ETC.

Statistical.

The proper study and interpretation of the returns of the Registrar-General should be augmented by special enquiry directed by the central body, because the special statistics already compiled and commented on, and especially those of the German and Dutch Cancer Committees, and those relating to Massachusetts, have not yet brought to light evidence free from ambiguous interpretation, nor have they the value which presumably would attach to the similar compilation based on the widely divergent races, regions, isolated communities, etc., which would come within the scope of the present enquiry, comprising as it will the whole British Empire.

The compilation of statistics would have to be conducted along the soundest

lines, and with regard to all conditions which may be supposed to favour the occurrence of malignant disease in man and animals.

Any scheme drawn up should be submitted to a statistical expert for approval.

A sufficiently extensive statistical enquiry may be expected to lead to the accumulation of facts helping to decide whether any form of disease comprised under the term "malignant" is communicable from one individual to another. It may further be of help in determining the direction enquiries as to the cause or causes are to take.

Owing to the time it will take to get together the mass of important evidence, which is waiting to be collected in different parts of the globe, I would suggest that early steps be taken to organise this collection.

I would divide into two great classes those to be relied upon for the immediate collection of the information sought, viz. those voluntarily assisting, and those who can be enlisted in the service through the different government offices and various local authorities.

It will thus be necessary at an early stage to ascertain how far the Local Government Board, India Office, Colonial Office, etc., town and county councils and other authorities having medical or veterinary officers in their services would be inclined to assist the enquiry.

Those voluntarily assisting would be essentially the staffs of hospitals and general practitioners. A direct appeal to each institution and individual seems desirable in order to direct attention to the special points on which definite information is wanted.

To avoid misapprehension, secure uniformity, intelligibility, and ready classification of the information obtained from such divergent sources as isolated Crown Colonies, Town and County communities, etc., definite questions should be asked. These being intended to elicit from distinct sources, both similar and different kinds of information, it would be necessary to draw up the various subjects of enquiry. In regard to this matter, advice might well be sought from the German Cancer Committee, who have already some experience of it.

In the interval that may elapse before the return of these enquiry forms, arrangements would have to be made for the classification and interpretation of the returns under the combined direction of a trained statistician and a director or other medical official.

Importance of Co-operation in Experimental Work.

In order to obtain the co-operation of skilled workers who would carry on special parts of the investigation at their own laboratories, etc., it would be necessary to arrange both for grants to them for their expenses, and for honoraria for their work. There are many who might thus be encouraged to assist the enquiry by undertaking special work on suggestions given to them by the central body, e.g., those who wish to use their work for the purpose of a graduation thesis at a University.

Of course, any work of this nature may be performed in any laboratory, the only condition being that the worker is fully qualified to undertake the work proposed, and that any control or suggestion on the part of the central body would be permitted by the chief of the laboratory in which the work is being done. In order to emphasise this side of the enquiry, circulars would have to be directed to all institutions likely to afford facilities for work of this nature, or, to provide such workers. The importance of central control would have to be emphasised, and the necessity for avoiding undue overlapping brought into prominence.

Importance of Study of "Malignancy."

The causes of, or changes which may accompany, or be responsible for, spread in the body must be investigated with especial care. This study may indicate the means by which power to spread may be removed, or may point the way to limitations in other directions. In this connection only the emaciation, secondary anæmia, and leucocytosis have received much attention. The not infrequent occurrence of pigmented moles, warts, etc., in albino and other animals seem to offer favourable conditions for a much more extensive investigation into the occurrence of other conceivable phenomena. Thus, the possibility of converting innocent conditions into malignant growths may be studied, and the importance of investigating the possible influence of internal secretions, by means of the injection, etc., of emulsions, watery and other extracts, fluids obtained under high pressure, or by means of a gelatine filter under high pressure from malignant growths must not be lost sight of. The study by recent methods, of changes in the serum and other fluids in cases where spread is occurring, or where an "innocent" tumour has become malignant, with a view to detecting there the presence of anything of the nature of an immune body, in Ehrlich's sense, must receive attention. It is impossible to express any opinion on the likelihood of being able by these means to ascertain the presence of factors which may cause spread, be concomitant with spread, or have really an antagonistic influence on spread.

Importance of properly controlling all Bio-chemical Enquiries in order to avoid fallacies and all tendency towards their assuming a too speculative nature.

Owing to the extreme complexity of the experimental methods necessary to this line of enquiry, it could only be carried out under the direction of one familiar with the methods, the manifold fallacies likely to present themselves, and the equally numerous control experiments necessary.

Granted due attention be paid to the above sources of error, purely hypothetical considerations must for the present suffice to suggest the following lines of enquiry.

A thorough scrutiny of malignant disease in the light of the knowledge which has been recently acquired in regard to hæmolysis, cytolysis, cyto-

toxines, immune-bodies, and the mechanism of their action, etc., ought to be undertaken.

The following special lines of enquiry also suggest themselves:—

A search should be made for evidence of anything arising pathologically, or experimentally, in consequence of the prolonged irritation of tissues, or the existence of cancerous conditions. Such evidence might be sought for in the existence of anything in the nature of excessive waste products, modified alkalinity of fluids, autolysines, isolysines, etc., such as it may be assumed might possibly stimulate local or general vegetative activity, or give rise to detectable excess, or deficiency of any constituent of cells, or of fluids. Also any evidence of local or general irritation arising from such causes should be sought.

An endeavour might be made to determine if the chemistry of the normal cell shows any divergence from that of the cancer cell which has developed from it. By means of modern methods applied to the albuminous bodies, ferments, etc., it might be possible to determine any divergence in the nature of the constituents of these cells; the presence or absence of normal or abnormal constituents might be sought for.

Hofmeister has recently pointed out the large number of distinct ferments contained in any one cell of the liver. It would be interesting to ascertain to what extent these ferments are present in the cells of malignant disease of this organ.

An enquiry might be instituted to determine if any stimulation of cells can be made to lead to the production in the latter of manifestations of activity with depression of the special function (secretion, motile phenomena, etc.), i.e., without calling forth what is regarded as the special function of the cells stimulated.

Classification and attempted Experimental Production of "Cancer."

In regard to the attempted experimental production of innocent and malignant new growths in animals, or the possibility of setting up the features of malignancy in benign growths, it may be well to repeat some old experiments, for example, in relation to embolism, etc., where the results obtained may have been vitiated by the conditions under which the experiments were at the time carried out.

In this connection the possible experimental production of "Petroleum cancer" and "Sweeps' cancer" would have to be borne in mind, and experiments carried out on a very wide series of differing species of animals.

The classification of different forms of cancer if properly carried out, might lead to the elimination of some forms which may be found to be due to special parasites (as for example, actinomycosis has been eliminated), and to the separating off of what may be found to be special types, or only seeming cancer. In all investigations of this nature full and detailed histological, chemical, bacterial, or other parasitic investigations must be made and a full history of each case clinically recorded.

The reputed transplantation of cancer into wound margins ought to be specially enquired into, with a view to the important bearing such an occurrence would have on other transplantation experiments. Such transplantation experiments should only be carried out with regard to the special species of animal in which the original growth occurred, and the special tissue in which it seemed to have had its origin. For all experiments of this nature the importance of the assistance of a trained veterinary man is very evident, for it would be especially necessary to exclude the possibility of previous infection.

A systematic study of the effects of persistent irritation of different epithelial surfaces in different species of animals might be found to have important bearings. In this category possibly the study of "Petroleum cancer" and "Sweeps' cancer" might be placed.

Those engaged in post-mortem examinations should be encouraged to search systematically for, and record all evidence of incipient or undetected malignant disease. Such an investigation might throw much light on the internal conditions, e.g., in the alimentary canal, which in themselves may perhaps lie long dormant, and in the end become malignant, in the same way as other conditions on the surface of the body are known to do.

A comparative study of mitosis and vegetative activity would require to be undertaken. Such an investigation would cover not only mitotic and vegetative activity in embryonic and cancer cells, but also that occurring in the cells of benign tumours, and of tissues which have reverted to an embryonic type in processes of repair, and with consideration of that overproduction which is an essential feature of repair.

I would respectively submit that any such scheme as the foregoing can only be provisional, and has been drawn up in full consciousness of the difference between drawing up a scheme on paper and putting the same into practice. I do not claim that this hastily drawn up scheme is adequate to cover the whole field of enquiry. In conclusion I would point out that the investigation must necessarily follow the lines which accumulated experience will dictate.

(Signed) E. F. BASHFORD.

Edinburgh,
October 24th, 1902.

III. 1937

In 1937, a distinguished group of investigators in the United States was asked to formulate a research program for the newly created National Cancer Institute. Their report was published in due time, and is revealing of the scientific consensus regarding cancer research of twenty years ago.

The Committee "tentatively proposed" that malignancy is a universal cell potentiality, that the degree of this potentiality is determined largely by hereditary factors, and that the malignant change of cells, which can be initiated by a variety of inciting agents that then are no longer required, ". . . appears to develop suddenly, becomes a fixed character, and is transmitted to its descendants. It gives evidence of being a somatic mutation."

The Committee noted that studies on chemical make-up, enzyme content, metabolism, or structure had failed to demonstrate differences between normal and cancer tissues. It considered established that mammalian cancer was not infectious, and grouped viruses with other microorganisms as etiologic agents that "may be disregarded," at least in the continuation of the process.

The Committee oriented its suggested research objectives to the investigation of the "causal genesis," or the inciting factors leading up to the development of malignancy, and of "formal genesis," or the nature of the cancer cell. For the former, emphasis was indicated for the study of heredity and of chemical carcinogenic agents. For the latter, it was urged that the field of cell physiology be developed, since ". . . the understanding of the process must be dependent on the advance in the understanding of growth and differentiation of normal cells."

The terms of reference of the Committee apparently were considered not to include clinical research. Nevertheless, it was recommended that research on therapy was justified, but required "a conservative and critical attitude." It also approved the development of clinical contacts for utilizing clinical problems for laboratory research and for testing methods suggested by laboratory experimentation.

FUNDAMENTAL CANCER RESEARCH [1]

Report of a Committee Appointed by the Surgeon General

In accordance with the National Cancer Institute Act, approved August 5, 1937, the purposes of which are set forth as "to provide for, foster, and aid in coordinating research relating to cancer; to establish the National Cancer Institute; and for other purposes," Surgeon General Parran appointed a committee of leading scientists to formulate, as far as this could be done, the fundamental aspects of the cancer problem and to suggest various lines of work which merit investigation.

This committee is composed of the following members:

Dr. Stanhope Bayne-Jones, professor of bacteriology and dean of the school of medicine, Yale University.

Dr. Ross G. Harrison, chairman of the National Research Council and Sterling professor of biology, Yale University.

Dr. Clarence C. Little, director, Roscoe B. Jackson Memorial Laboratory.

Dr. John Northrop, member, Rockefeller Institute for Medical Research.

Dr. James B. Murphy, member, Rockefeller Institute for Medical Research, chairman.

The text of the report prepared by this committee follows.

During the past 30 years of extensive investigation into the problem of cancer, sufficient information has accumulated to justify an attempt at a formulation and clarification of this material that will serve as a basis for future investigation. Three main lines of attack have contributed definite fundamental facts regarding the nature of malignancy, but the difficulty in the past has been that each of these three lines of investigation has been developed independently, taking little account of the knowledge gained in the other fields.

What appear to be the more fundamental data have been selected here and tentative conclusions have been drawn as a basis for discussion. The three lines which have yielded the data for analysis are:

I. The study of transplantable tumors which has yielded information on the biology of the malignant cell;

II. The conditions governing the experimental induction of malignant tumors;

III. The part played by genetic factors in the development of cancer.

I. BIOLOGY OF THE CANCER CELL

Whatever may be the contributing cause, malignancy once acquired becomes a fixed character of the cell. As shown by the study of transplants in animals and in tissue culture, the continuation of the condition is not dependent on the factors which were responsible for its development.

[1] Reprinted from Public Health Reports 53: 2121-2130, 1938.

The cells will continue their malignant course uninterruptedly without the continued presence of carcinogenic agents in hosts without endocrine disturbance, liver dysfunction, or action of estrogenic hormones. For instance, transplanted mammary gland cancer grows as well in the male and castrated animal as in the female. Not only does the malignant state become a fixed character, but the type, the tendency to distinct histological arrangement, growth rate, invasiveness, and general behavior are more or less constant for each tumor.

All of this points to the conclusion that malignancy once it is established in a cell becomes an automatic process independent of the presence of a continuously acting agent of outside origin, that the new character of the cell becomes a fixed one which is passed unchanged to the descendants.

Attempts to establish fundamental differences between normal and malignant cells of the same tissue type have failed to bring out any striking variation in chemical make-up, enzyme content, metabolism, or structure. Even transplantation is limited by the same laws as those governing normal tissues, and factors which influence the growth of cancer grafts are equally effective in their influence on the growth of normal tissue grafts. It has not been proved that cancer cells are more sensitive to the action of physical agents (heat, cold, X-ray, or radium) than normal cells of the same type. Even function (secretion) may not be interfered with by the development of malignancy. Possible exceptions to these general statements are: (*a*) Individuality differentials may act in transplantability of normal tissues but not in tumors; (*b*) differences in metabolism (oxidation) between tumors and normal tissues.

Mammalian cancer can be transmitted only by grafts of living tumor cells, and the cells of the host do not become malignant by intimate contact with the cells for which it supplies blood vessels and supporting stroma. The very exhaustive study of mammalian cancer has disclosed a complete lack of evidence of its infectious nature. It has been definitely shown that the animal parasites and bacteria, which may incite malignancy in other organisms, play no part in the continuation of the process. The present evidence tends to indicate that the same may be true for the viruses. As causes of the continuation of the malignant process the many microorganisms which have been described as specific etiological agents may be disregarded.

These findings indicate that malignancy is the result of a fundamental change in cell physiology.

II. PRESENT STATUS OF CARCINOGENIC AGENT STUDY

The isolation and identification of the particular group of compounds present in coal tar which are responsible for its carcinogenic action have led to a concentration of interest in the induction of malignant tumors. The structural relationship of these particular hydrocarbons to certain compounds naturally occurring in the living animal has stimulated extensive investigation of the possibility that these natural substances may act, under certain conditions, as carcinogenic agents or may be

transformed by some abnormal condition in the body into active carcinogenic substances. Important as these observations are in evaluating the deductions which may be drawn, proper consideration should be given to the fact that there are many other potent carcinogenic agents entirely unrelated chemically to these hydrocarbons. The simple chemicals, such as arsenic and chloride of zinc, may induce malignant changes. The biological agents, parasites (notably tape worms in their cystic form in the liver, Bilharzia infection of the bladder), germs, tubercle bacilli, particularly in infection of the skin, the syphilis organism, notably in mouth infections, may induce malignancy. Recently it has been demonstrated that under special conditions a virus may act in very much the same way as do the chemical carcinogenic agents. That is, it appears to start a chain of events which tend to go over into malignancy; but there is as yet no evidence that the maintenance of malignancy is dependent on the continued presence of the virus.

The first deduction derived from the experimental study of carcinogenic agents, namely, that the process was one of simple chronic irritation, may probably be definitely discarded. The most active agents are practically devoid of irritative action in the strict sense of the word. There is perhaps sufficient evidence to indicate that they are not cell stimulants, but that they actually tend to inhibit the growth of cells.

The general conclusions which may be drawn from this extensive study are as follows: (1) So-called carcinogenic agents appear to start a process which may lead to malignancy; but once the process is started, the agents apparently play no further role in the picture. Examples: X-ray cancer, cancer of the skin from external application of coal tar; the disappearance of active virus from papilloma before malignancy appears. In fact, the malignancy may occur months or even years after the exposure to the carcinogenic agent. (2) Almost all, if not all, classes of cells may be rendered malignant under the influence of one or more agents. Not only may this be concluded from the fact that among naturally occurring tumors practically all types of cells are represented, but malignancy has been induced experimentally in skin, connective tissue, liver, lungs, stomach, gall bladder, kidney, testicle, muscle, bone, bone marrow, lymphoid cells, the uterus, mammary gland, and other tissues. It may be deduced from this that malignancy is a universal cell potentiality. (3) The expectation that with the method of inducing tumors it would be possible to trace the transformation of normal cells into malignant cells has not yet been realized. In the area of tissue disturbance induced by the agents a new race of cells appears quite suddenly with no apparent gradation.

The general systemic effect of carcinogenic agents has not yet received adequate consideration. It has been shown that the simple application of coal tar to the skin of an animal will produce general changes in the internal organs, particularly the lymphoid system and the liver, changes indistinguishable from those produced by a generalized exposure to the X-ray. The application of either of these agents causes a distinct lowering

of resistance to transplants of cancer and may break down a highly developed resistance to the growth of cancer cells. Injections of the chemical agents, even in small amounts, cause a marked increase of a natural tendency in certain strains to develop tumors of certain organs (cancer of lung), or in the rabbit, accompanying the liver and lymphoid damage, there is a tendency to tumor formation in the uterus. The active hydrocarbons of coal tar injected into immature animals cause a permanent stunting of growth.

Recently a virus (the Shope virus) has been discovered in cottontail rabbits which produces papillomas and which is capable of inducing similar growths in domestic rabbits. These growths in domestic rabbits enlarge with great rapidity and frequently become cancerous as seldom happens in the cottontails. Yet from the majority of the papillomas of domestic rabbits the virus cannot be recovered, nor has it ever been gotten from the cancer. The present state of the investigation of this interesting material does not disclose the part which the virus plays in cancer etiology.

While the active virus has not been demonstrated in cancers arising in virus-induced papillomas its presence has been indicated indirectly by serological methods. The virus injected intravenously will readily localize in areas of skin previously treated with coal tar and will cause a malignant change much earlier and more frequently than would be the case with tar alone. When acting in this way it appears to be the precipitating factor in cancer. The virus will also localize in cell proliferations caused by noncarcinogenic agents and no malignant changes result. The question is still unsettled as to whether the cancers induced by the virus in tarred skin may not be entirely due to a stimulating effect upon cells already rendered malignant by the tar.

From the virus point of view the fowl tumors still continue to furnish material of the greatest importance. Here the transmitting agents apparently cause a direct transformation of normal into malignant cells, and the continuation of the process seems to depend on the continued presence of the transmitting agent. So far no agents have been procured by the extensive investigation of mammalian tumors with which cancer can be directly transmitted, but the possibility that such a substance or substances do exist in mammalian tumors is certainly worthy of future consideration. The difficulty in their demonstration may be due to the relative impenetrability of the mammalian cell or the agents may be less stable than those from the fowl tumors. A notable property of the group of agents causing tumors of fowls is that they not only stimulate proliferation of cells, but also cause differentiation of the cells into complex tissue organizations. This property, in addition to some others, has opened the question as to whether this group of agents is of endogenous origin. In any case it seems unjustifiable at the present time to draw any conclusions as to tumors in general from the behavior of this group.

III. HEREDITARY FACTORS IN MALIGNANCY

The first contribution in this field was the observation that families of mice having a markedly higher cancer rate than the average for a mixed population could be segregated. The tendency to develop cancer in a given family is confined, for the most part, to an organ or special tissue, so that we have lung cancer families, mammary cancer families, sarcoma families, and the like. This inherited tendency is not that of a generally unstable cell system, as shown by the fact that a strain showing a high cancer rate for the lung or the breast will often prove more refractory to induced cancer of the skin than strains having a very low cancer rate. The tendency for cancers to form in a definite organ or tissue may be accentuated by environmental conditions. For example, mammary gland tumor rate in mice may be increased by intensive breeding, by mammary duct blockage, or by excessive dosage of theelin, and the lung tumor rate may be increased by the surface application or subcutaneous injection of chemical carcinogenic agents. In the latter instance, whether the agents are absorbed and act directly on lung cells or whether the tumors result from the release of the inherited tendency by a lowering of general resistance is undetermined. The present indications are that the type of inheritance is not the same for different strains of tumor. Cancer of the lung appears to be dependent more directly on genetic influence, whereas the inherited tendency to cancer of the breast is transmitted in greater intensity by the female than by the male, which suggests a supplementary hormonal or extrachromosomal influence.

Regardless of the nature of the inheritance, it would appear that the manifestations are the same. The inherited state is an unstable or poorly balanced cell system confined to an organ or tissue type, in which the specific cells tend to become malignant either from functional strain or from unfavorable environmental conditions. This response to physiologic strain is illustrated by the following facts: The females of a family of mice which, under normal breeding conditions, give a high rate of cancer of the breast will show an increased rate if subjected to forced breeding. If the females of such a strain are prevented from breeding the rate may be very low. For example, one strain, which gives a rate of 70 to 80 percent among the normally breeding females, showed only 12 percent in the virgin females. Prepuberty castration reduces the rate to a negligible one. The males of such strains castrated in early life and engrafted with ovaries or injected with estrogenic compounds will develop mammary tumors about as often as do the virgin females. Families not inheriting a natural tendency do not develop cancer from overstimulation with estrogenic hormones or breast blockage.

Another example of the variation in threshold effect is found in the lung cancer families where, in hybrids of varying degree of tendency to spontaneous lung cancer, the particular degree of susceptibility is paralleled by the percentage in which lung tumor may be induced by carcinogenic agents.

Whatever the mode of inheritance of the cancer tendency, the condition inherited seems to be a poorly balanced cell system or cells with a higher

potentiality for malignancy. The condition responsible for the initiation of the process likewise may be inherited (endocrine unbalance) or it may be an outside agent (lung tumors).

The following formulations or definitions may be tentatively proposed:

1. Malignancy is a universal cell potentiality, in that any cell has inherent in its make-up the potentiality for unlimited or uncontrolled growth.

2. The degree of the potentiality for malignancy is a variable quantity for each tissue or cell type and this degree is determined largely, if not entirely, by hereditary factors.

3. The malignancy potentiality of a cell may be developed in the more sensitive groups by the strain of normal physiological processes but may be set off even in resistant groups by a variety of inciting agents.

4. The change from a normal to a malignant cell represents an alteration in the cell itself by virtue of which proliferation becomes an automatic process independent of the presence of a continuously acting provocative agent.

5. The new property of the cell appears to develop suddenly, becomes a fixed character, and is transmitted to its descendents. It gives evidence of being a somatic mutation.

RESEARCH OBJECTIVES

For the practical purpose of investigation, the cancer question may be divided into two distinct objectives: First, the *causal genesis* of tumors, including the inciting causes leading up to the development of malignancy, and, second, the *formal genesis*, or the factors responsible for the nature of the cancer cell and its tendency for unlimited multiplication. These objectives may be combined or kept distinct from each other, but they should be considered and properly adjusted in the planning and conduct of any experiment.

For the first problem, the causal genesis, there are sufficient data to indicate that there are multiple and diverse causal conditions and that these probably vary for each type of cancer. This diversity of causes is sufficiently distinct to justify investigating the different types almost as if they represented different diseases. For the second, or formal genesis of cancer, if the present conceptions are correct, the changes in the cell responsible for the state give evidence of being the same regardless of the cause. The different manifestations of the disease appear to be dependent on the degree of malignancy, the type of cell affected, and the environment (location, physical condition of the host, and the amount of resistance). The agents concerned in the causal genesis do not at present appear to play any part in continuation of the malignant state or to influence the final outcome.

CAUSAL GENESIS

For the investigation of the causal genesis the following fields are indicated in the light of present knowledge:

Heredity.—Based on the evidence of the prominent part played by

the degree of potentiality for malignancy exhibited by cell groups in different strains of animals, the relative importance of heredity warrants intensive investigation with particular stress on the different cancer types. From the practical side this general field has assumed an importance, for it is probable that preventive measures will come from knowledge gained from this type of investigation. Already such leads have been opened up as the demonstration that the mode of inheritance is not the same for all tumor types; that an inherited tendency for endocrine disturbance may be the determining factor in at least one type of cancer; that liver dysfunction may be prominent in another; that induction of mammary tumors by the estrogenic hormones is definitely correlated with the inherited tendency to breast tumor; that, in general, the ease with which a tumor may be induced experimentally depends on the genetic make-up of the host.

In this connection it has become evident that pure strains of animals of known hereditary tendencies are as important for cancer research as pure chemicals are for the chemist.

It is equally evident that the development of this important line of investigation should include continued study of the particular influence and nature of inheritance for each of the major types available for observation. Since experimenters have come to realize that different factors are operative in different types of tumors, it has become progressively more probable that much light may be thrown on the tumor problem.

A comprehensive study of the incidence of cancer in men with reference to both environmental and hereditary factors should be made. Such a study should be based on clinical data and family histories built upon direct observational methods. In the analysis of the hereditary factors advantage should be taken of the recently developed statistical methods for the detection of linkages.

The carcinogenic agents.—There already exists a formidable list of chemical, physical, and biological agents, including viruses, which are known to initiate conditions tending to go into a malignant state. It is a question as to how useful it will be to extend this list unless the effort is directed more toward finding agents which may have some connection with the naturally occurring human tumors. The greatest need in this field is the development of an investigation directed toward the clarification of the mode of action of these diversified agents rather than a search for more agents. However, the possibility exists that some yet undiscovered agent may supply the key to the understanding of the mode of action.

There are two possible leads which might be the entering wedge in the study of this problem of mode of action: One is the fact that several prominent representatives of the chemical group do not act primarily as stimulators of growth but actually inhibit growth even in high dilutions. If this property is common to the various types of agents known to incite cancer (and this should be determined), it should be possible to establish

the particular effect on cell metabolism or other factors responsible for this action. It is important to determine whether prolonged inhibition of cells may not tend to produce mutants with excessive growth capacity.

The second lead is based on the fact that another property of several of the carcinogenic agents, perhaps of all of them, is their general effect on the animal body, even when the applications are made on the unbroken skin. These changes are not fully determined but prominent among them are disintegration of the lymphoid tissue, liver damage, uterine changes, and undoubtedly other effects. Among the agents, tar, X-ray, and the pure carcinogenic hydrocarbons have been found to lower an animal's resistance to the growth of cancer cells. Such observations may open up the question as to whether a carcinogenic agent is effective because of a dual action, inciting a local cell derangement and a disturbance of the body's mechanism for dealing with such a disturbance.

Whether or not the foregoing leads prove of importance, there is no question about the advisability of directing an effort toward learning the mode of action of the carcinogenic agents, and also of the importance of keeping the investigation in the general realm of agents which have a part in the naturally occurring disease.

Somewhere between the inherited or acquired cell tendency and the factor which releases this tendency lies the crux of the cancer problem as far as the inception of the disease is concerned.

FORMAL GENESIS

The fundamental problem in cancer still continues to be the formal genesis of the cancer cell. The evidence that whatever may be the part played by the various factors, and however different these factors may be for different tumor types, the end result is the same—a cell with a capacity for unlimited or uncontrolled growth. Have they become "fast" to the conditions which normally control cell growth in the body or is there a break in the internal control mechanism of the cell, or is there a loss in body control of cell activity? This, the core of the problem, has been almost entirely neglected. As there is an apparent lack of appeal to workers it may be necessary to foster the development of an investigation along this line.

This investigation of characteristics of the cancer cell belongs in the field of cell physiology, and the understanding of the process must be dependent on the advance in the understanding of growth and differentiation of normal cells. But, as in general the knowledge of function (for example, the glands of internal secretion) has been gained largely by the study of dysfunction, should not the cancer cell be for the cell physiologist what the acromegalic or the cretin is for the glandular physiologist?

This field requires definite nurturing and it is felt that an important function would be served if this line of investigation were stressed.

The recognized limitations of cancer therapy justify carefully planned and executed animal experimental work aiming at the discovery of new therapeutic agents. Reference is made in this connection to newly dis-

covered artificially produced radio-active isotopes, bacterial filtrates, tissue extracts, and certain synthetic organic chemicals, which may possess therapeutic properties. In order to avoid the many pitfalls, a conservative and critical attitude is particularly essential in work along this line.

The Committee approves the plans of the National Cancer Institute for developing its clinical contacts and recommends that this development proceed, with a view to detecting and utilizing clinical problems for research in the laboratory, and to testing in the clinic promising methods suggested by laboratory experimentation.

In any program for cancer research, patience and the adoption of a long-time point of view are absolutely essential.

IV. 1957

The National Cancer Institute is now twenty years old; the Imperial Cancer Fund, fifty-four. Were another Committee to formulate a program of cancer research, what discoveries of the past twenty years would it have to consider, and what directions would it perhaps indicate?

The question invites discussion, in which the ideas of any one individual should be considered as personal views. In my opinion, the following findings and areas for further inquiry have particularly timely relevance in that they seem most likely to make significant contributions to the prevention and treatment of cancer.

First, as to causation, the role of viruses in cancer, discovered by Peyton Rous in 1911, must again be considered in the forefront of etiologic possibilities. To the Shope rabbit virus and the Bittner mouse virus have been added more complex relationships to viruses that are involved in mouse leukemia. If cancer is indeed a cellular aberration due to the presence of an intracellular virus, the technological advances in the study of virus diseases during the past two decades stand ready to be applied with renewed vigor to the cancer problem in man as well as in animals. For these investigations, as well as other research, the improving techniques of tissue culture and the new observations on heterotransplantation will continue to be of increasing importance.

Research on chemicals and physical agents that are capable of evoking the neoplastic reaction has been extended to a wider investigation of environmental carcinogenesis. Thus, the useful empirical endeavors introduced into the cancer field by Percival Pott in 1775 have regained attention. It is now clear that there are many important carcinogenic situations to which human populations outside of industrial environments are liable. Tobacco smoking, especially of cigarettes, is established as one of the causes of epidermoid lung cancer. Atmospheric pollutants of industrial and individual sources have been shown to include materials able to evoke cancer in animals, and presumably also in man Ionizing radiation, even in doses used for diagnostic purposes in pregnant women, increases the incidence of leukemia in their children. At higher doses it produces leukemia, cancer of the thyroid, and probably several other types of neoplasms in addition to the skin carcinomas that have claimed victims since the turn of the century The more subtle inverse relationships of circumcision and cancer of the penis and of the uterine cervix, of dietary deprivation and hepatic cancer, of socio-economic gradients in cancer of the esophagus and of the stomach, are exciting challenges to research, in which statistics, clinical studies, laboratory experiments, and practical public-health measures all have a role

Second, as to the nature of the neoplastic transformation. It can be considered as established that cancer is a disease of the cell. To the extensive evidence that has accumulated since the turn of the century, several recent findings are of particular interest. Cells grown in tissue culture can acquire neoplastic characteristics, as described by Earle and

by Gey. Leukemia can be transmitted from one mouse to another by the transplantation of a single cell, as reported by Furth.

It is now probable that the neoplastic process is not a single event that endows cells with immutable, full-blown malignant characters. The stepwise, slow development of many neoplastic entities in man as well as in animals has now been amply demonstrated. The progression of dependent neoplasms through conditioned phases to eventual full-blown autonomous neoplasia in mice has been well documented, particularly for tumors arising from hormone-responsive tissues. In man, the transition of rectal polyps to carcinoma, and of "carcinoma-in-situ" of the uterine cervix to the invasive neoplasm may represent analogous gradual acquisition of new characters by cell populations. Papanicolaou's contribution of exfoliative cytology has developed into a practical early diagnostic procedure applicable to public health. The effect of this concept extends also to treatment. The logical course that is open in the face of a single, irreversible cellular change is to find it and to destroy it. Gradual transformation over a decade allows consideration of more leisurely physiologic modifications that might regress, arrest, or retard the process.

Third, in regard to treatment. As recorded by Beatson in 1896 for breast cancer and demonstrated by Huggins in 1941 for prostatic cancer in man, the progress of certain neoplasms is at least partially reversible, even when it has reached the metastatic stage. To the observations on tumors derived from hormone-dependent tissues have been added the partially differential effects of antimetabolites and of alkylating chemicals on tumors of the lymphatic and hematopoietic systems. As short a time ago as 1945, Woglom likened the search for chemotherapeutic agents against cancer to the search for materials that on intravenous administration would dissolve away the left ear and leave the right one undamaged. Sufficient data are at hand to suggest that this degree of pessimism may be unjustified and that semi-empirical searches for therapeutic agents may yield at least partially effective measures for a number of neoplastic diseases.

It is probable, however, that the general definitions of the problem and the suggestions about research approaches, as embodied in the three historical statements reproduced here, would be accepted by many investigators of cancer as being still valid. The fundamental problem of cancer as a cellular alteration remains as obscure now as it was twenty years ago. Undoubtedly, the newer techniques of electron microscopy, of fractionation of cells, of electrophoretic and chromatographic analyses, of histochemistry, and of tracer studies in metabolism have opened new dimensions in biological research. The contributions of these investigations to cancer, however, are difficult to interpret. Nevertheless, these may be the areas of research from which the most significant contributions eventually applicable to the prevention and treatment of cancer are likely to arise.

It is heartening to observe and to acknowledge the ever-widening scope of scientific interest that continues to be applied to the cancer problem. This has been made possible in no small measure by the wise, tolerant

administrative leadership of cancer research programs and the generous, far-sighted financial support that has been extended to cancer research.

The admonition of the Committee of 1937, that " . . . patience and the adoption of a long-time point of view are absolutely essential." remains timely, but an optimistic viewpoint now appears more justified than ever before. Perhaps we can even look forward to fulfilling the intention of the Committee of 1802, " . . . to obtain a remedy for a most painful and dreadful disease."

J. W. SCHERESCHEWSKY

1873–1940

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J. W. Schereschewsky: An Appreciation

H. B. ANDERVONT, *National Cancer Institute, Bethesda, Maryland*

DR. Joseph W. Schereschewsky receives recognition in this number of the *Journal* because his interest in cancer as a public health problem did much to stimulate passage of the Cancer Act. His friends and associates of the years preceding 1937 welcome this opportunity to place on record his devotion to medical science and his loyalty to the Public Health Service. The following brief historical account is prepared from the accumulated memories of a few who knew and worked with him during those early years.

In 1922, Dr. Schereschewsky proposed to the Surgeon General that the Public Health Service inaugurate a program of cancer research. The idea was accepted, but it was deemed essential that a preliminary survey be conducted to establish the disease as a major problem in public health and thus justify the attention of the Service. Dr. Schereschewsky was given this assignment with the privilege to choose the location for the work. An invitation from Dr. M. J. Rosenau, Professor of Preventive Medicine and Hygiene at the Harvard Medical School, and a fondness for New England were the chief factors in his decision to locate in Boston.

He accepted the assignment with his usual vigor and sagacity, for, within three years, he published *Public Health Bulletin No. 155* [1] showing an increase in cancer mortality, over a period of twenty years, in a large part of the registration area of the United States. This *Bulletin*, with an appendix by Dr. E. B. Wilson, Professor of Vital Statistics of the Harvard School of Public Health, is a classic in its field. The first and last two paragraphs are presented here because they reveal far better than the words of others Dr. Schereschewsky's forcefulness and clarity of expression, his breadth of outlook, and his devotion to duty.

> "The striking observation about cancer mortality has been its apparent steady increase from year to year. This phenomenon challenges the attention whenever the cancer statistics of nearly all civilized countries are reviewed.
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> . . . . . .
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> "As to the causes which have led to the steady increase in the cancer mortality, here one can do not more than to speculate. Since, however, it has been shown, with a considerable degree of probability, that we are facing an actual and not apparent increase, this is evidently a promising

[1] SCHERESCHEWSKY, J. W.: The course of cancer mortality in the ten original registration states for the 21-year period, 1900–1920. Pub. Health Bull. No. 155. Treasury Department, United States Public Health Service, Washington, D. C., 1925.

field for epidemiologic study which, as one ventures to hope, may throw much light upon the so far baffling etiology of cancer. The question at once arises, 'What progressive factor or factors characteristic of modern phases of social organization and development have been operative to cause this increase?' Determined assiduity in all phases of this problem may still yield the answer.

"That the cancer death rate will continue to increase in the future as it has in the past is not to be supposed. Physical, chemical, and biologic processes all tend to a state of equilibrium. So in the case of cancer when the forces which are tending to raise the human race to a new and higher level of susceptibility have spent themselves, we may expect no further increase in the rate, at least from the operations of these causes. And, lying concealed in these evils, as in Pandora's Box, there is still hope in the hearts of the medical profession and of the students of the public health that to-morrow, next month, or next year the true defense against this relentless foe will be vouchsafed us."

His last publication [2] dealing with the control of cancer appeared in 1938, one year after his retirement from the Service, when he was also organizing a cancer control program for the State of Georgia. The concluding paragraphs of this paper show a realization of the magnitude of the problem and a subtle sense of humor appreciated by all his friends.

"The thoroughgoing Nation-wide application of such control measures should eventually effect a reduction of 25 to 30 percent in the cancer mortality rate, representing an annual saving of about 35,000 lives. This would offset the mortality due to automobile accidents.

"The probable annual cost of such a Nation-wide attack upon cancer to the States would be in the neighborhood of $10,000,000."

The 1925 publication by Dr. Schereschewsky was an important factor in the increasing interest in cancer research. The Public Health Service expanded its cancer studies in Boston. Dr. Rosenau generously supplied the necessary laboratory space in his department and, beginning in September, 1930, Dr. Schereschewsky recruited a small group of young, enthusiastic investigators to conduct basic cancer research in biology, chemistry, and physics. The activity of this group resulted in about thirty-five publications prior to December 31, 1937. Seldom, if ever, did Dr. Schereschewsky's name appear on any of these papers despite the fact that his advice, encouragement, and criticism played an important part in every experiment. He knew how to handle young scientists. He was a firm believer in freedom of research and all who came with him were told bluntly that they were to conduct independent research and "It is up to you to sink or swim."

He emphasized two approaches to the problem. The first was basic research on the nature of the cancer process through the study of the disease in experimental animals. He opposed the close association between this type of research and the clinic because, in his opinion, too little was known of the nature of the disease to expect any rapid application of results to the disease in man and because patient care could submerge the experimental approach. Furthermore, in times of financial stringency,

[2] SCHERESCHEWSKY, J. W.: The prevention and control of cancer: A plan for nation-wide organization. Pub. Health Rep. 53: 961–969, 1938.

basic studies could be the most vulnerable to reduced support. The second was an intensive study of the epidemiology of the disease in man. He deplored the lack of this approach and was convinced that this should be the major contribution of the Public Health Service to cancer control. Indeed, he felt strongly that " . . . epidemiological study . . . may throw much light upon the so far baffling etiology of cancer."

From 1930 to his retirement from the Service in 1937, his major objective was the establishment of a cancer research center within the Public Health Service. Those close to him were fully aware of the extensive correspondence and his frequent trips to Washington in this connection. His conviction that cancer was a major public health problem and that the Service would meet the challenge never wavered, even when his activities received a drastic budget cut during the depression years. The writer recalls the following words from him upon his return from a visit to Washington. "If the Service goes into cancer in a big way before I retire, my job will be done."

Dr. Schereschewsky was born in China in 1873. His father, a man of high cultural achievements, was a missionary who became Protestant Episcopal Bishop of China. Dr. Schereschewsky obtained an A. B. degree from Harvard in 1895 and an M. D. degree from Dartmouth in 1899. His medical training was interrupted by enlistment in the Army Medical Corps during the Spanish-American War. He served in Cuba and almost died after contracting yellow fever.

He was commissioned in the Public Health Service in 1899 and served with distinction as Officer in Charge of: Field Investigations of Occupational Disease, from 1913 to 1918; Division of Scientific Research, from 1918 to 1922; and Office of Cancer Investigations, from 1922 to 1937.

He was endowed with a striking personality, and through his devotion to medical science inspired those who worked with him. His outstanding characteristics were a remarkable versatility, an exceptional memory, and a fertile imagination. Versatility was a common trait in scientists of his generation but, in this respect, he was a constant surprise to even his closest associates. His knowledge included all cultural subjects, sports, and mechanics, and he displayed an intense interest in current events. He possessed an amazing ability to concentrate and, during these periods that lasted for days, weeks, or months, his associates soon learned the futility of any effort to interrupt his thoughts or activity.

Events of the past twenty years have confirmed his farsightedness in recognizing cancer as a major field of interest to the Public Health Service and in stressing the basic science approach to the problems of malignant disease.

APPENDIX

National Advisory Cancer Council

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Assistant to the Secretary of Defense (Health and Medical)
Department of Defense
Washington, D. C. (Represented by Capt. Wm. Silliphant (MC) USN Director, Armed Forces Institute of Pathology, Walter Reed Army Medical Center (Member *ex officio*)

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Chairman of the Board
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Morris Plains, N. J.
October 1953–September 1957

Dr. Leroy E. Burney, Surgeon General
U. S. Public Health Service
Washington, D. C.
(Member *ex officio* and *chairman*)

Dr. Sidney Farber
Director of Research
Children's Cancer Research Foundation
Boston, Mass.
October 1953–September 1957

Mr. Donald E. Johnson
Publisher, Flint News-Advertiser
Flint, Mich.
October 1953–September 1957

Mrs. Albert D. Lasker
Albert & Mary Lasker Foundation, Inc.
New York, N. Y.
October 1954–September 1958

Dr. William Middleton, Chief Medical Director
Department of Medicine and Surgery
Veterans Administration
Washington, D. C. (Represented by Dr. G. R. Callender, Director of Pathology and Allied Sciences, Veterans Administration) (Member *ex officio*)

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Vice Chancellor
Schools of the Health Professions
University of Pittsburgh
Pittsburgh, Penna.
October 1954–September 1959

Dr. Isidor S. Ravdin
Chairman, Department of Surgery
University of Pennsylvania School of Medicine
Philadelphia, Penna.
October 1954–September 1958

Dr. Leo G. Rigler
Professor of Radiology
University of Minnesota School of Medicine
Minneapolis, Minn.
October 1955–September 1959

Dr. Joseph F. Ross
Associate Dean and Professor of Medicine
University of California Medical Center
Los Angeles, Calif.
October 1956–September 1960

Dr. H. P. Rusch
Director, McArdle Memorial Laboratory for Cancer Research
University of Wisconsin
Madison, Wis.
October 1954–September 1958

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Director, Kerr-McGee Oil Industries, Inc.
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Director, Division of Natural Sciences
Rockefeller Foundation
New York, N. Y.
May 1957–September 1960

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Associate Professor of Clinical Surgery
Medical College, Cornell University
New York, N. Y.
January 1945–December 1947

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October 1950–September 1953

Dr. Joseph C. Aub
Professor of Research Medicine
Harvard Medical School
Boston, Mass.
October 1951–September 1955

Dr. Edward Chamberlain
Professor of Radiology
Temple University School of Medicine
Philadelphia, Penna.
October 1951–September 1955

Dr. Arthur Compton
Professor of Physics
University of Chicago
Chicago, Ill.
October 1937–October 1940
and
January 1942–December 1944

Dr. James B. Conant
President, Harvard University
Cambridge, Mass.
October 1937–October 1940

Dr. Max Cutler
Director, Chicago Tumor Institute
Chicago, Ill.
December 1939–December 1942

See footnotes on page 338.

Dr. Edward A. Doisy
Professor of Biological Chemistry
St. Louis University School of Medicine
St. Louis, Mo.
November 1940–November 1943
January 1948–September 1950†
and
October 1950–September 1952

Dr. James Ewing‡
Director, Memorial Hospital for the Treatment of Cancer and Allied Diseases
New York, N. Y.
October 1937–October 1938

Dr. Wm. U. Gardner
Professor of Anatomy
Yale University School of Medicine
New Haven, Conn.
January 1950–September 1950†
and
October 1950–September 1954

Dr. Lowell S. Goin
Chief, Dept. of Radiology
Queen of Angels Hospital
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January 1949–September 1950†
and
October 1950–September 1951

Mr. Maurice Goldblatt
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Harvard University
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January 1943–December 1945

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Rush Medical College
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October 1937–October 1939

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Surgeon-in-charge
St. Elizabeth's Hospital
Richmond, Va.
December 1943–December 1944

Dr. Charles B. Huggins
Professor of Surgery
School of Medicine,
University of Chicago
Chicago, Ill.
January 1946–December 1948

Dr. A. C. Ivy
Nathan Smith Davis Professor of Pharmacology and Physiology
Medical School, Northwestern University
Chicago, Ill.
January 1945–December 1947

Dr. C. C. Little
Director, Roscoe B. Jackson Memorial Laboratory
Bar Harbor, Maine
November 1937–November 1939

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Wilmerding, Penna.
February 1951–September 1952

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Roving Editor, Reader's Digest
1088 Park Avenue
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October 1950–September 1953

Dr. Sherwood Moore
Director, Mallinckrodt Institute of Radiology
Washington University
St. Louis, Mo.
January 1944–December 1946

See footnotes on page 338.

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Professor of Surgery
University of Rochester,
School of Medicine and Dentistry
Rochester, N. Y.
January 1948–September 1950†
and
October 1950–September 1954

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Vice President, American Cancer Society
Seattle, Wash.
October 1951–September 1952

Dr. James B. Murphy‡
Member in Charge of Cancer Research
Rockefeller Institute for Medical Research
New York, N. Y.
December 1938–November 1941
and
January 1943–December 1945

Dr. Thomas Parran
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August 1937–April 1948

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October 1951–September 1955

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Professor of Surgery
University of Cincinnati Medical School
Cincinnati, Ohio
December 1938–November 1941
and
January 1943–May 1943

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Director, Memorial Hospital for the Treatment of Cancer and Allied Diseases
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November 1940–November 1943

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April 1948–August 1956

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Yale University School of Medicine
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November 1939–November 1942
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January 1944–December 1946

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Professor of Biochemistry
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Berkeley, Calif.
October 1952–September 1956

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Associate Professor Pathology
School of Medicine
University of Chicago
Chicago, Ill.
January 1950–September 1950†
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October 1950–September 1953

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University of California Medical School
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November 1946–December 1948

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Mayo Clinic
Rochester, Minn.
January 1942–August 1942
and
January 1947–December 1949

Dr. Shields Warren
Assistant Professor of Pathology
Harvard University Medical School
Boston, Mass.
January 1947–December 1949

Dr. Frances Carter Wood‡
Director, Institute of Cancer Research
Columbia University
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November 1937–November 1938

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*Position listed after name is the one held at time of appointment.

†Public Law 692, 81st Congress, increased the number of members of the National Advisory Cancer Council, changed the term to four years, and terminated the appointments of all members serving under the provisions of the previous legislation. All members whose terms were thus terminated were reappointed for a term of one, two, three, or four years under the new law.

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Published by the U. S. Department of Health, Education, and Welfare in accordance with section 220, title 44, U. S. Code

Use of funds for printing this publication approved by the Director of the Bureau of the Budget, May 14, 1956

UNITED STATES GOVERNMENT PRINTING OFFICE, WASHINGTON : 1957

For sale by the Superintendent of Documents, U. S. Government Printing Office
Washington 25, D. C. - Price per copy $2.00

Subscription price for two volumes per year in the United States, Canada, and Mexico, $20.00; foreign, $25.00

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